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Impact of Rotavirus Vaccination on Intussusception Hospital Admissions in England.

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ABSTRACT

Background

An increased risk of intussusception has been reported following rotavirus vaccination. We sought to determine whether introduction of rotavirus vaccination in England in July 2013 was associated with a change in the burden of total and age group-specific childhood hospital admissions for intussusception.

Methods

We identified all children aged 0-36 months admitted to hospitals in England with intussusception using the Hospital Episode Statistics dataset. We performed a retrospective ecological analysis comparing hospital admission rates for intussusception during the periods before (2008/2009 - 2012/2013) and after (2014/2015 - 2017/2018) introduction of rotavirus vaccination using modified Poisson regression and interrupted time series analysis. Length of hospital stay and clinical outcomes were also examined.

Results

The mean annual admission rate for intussusception in infants over the ten-year study period was 31.5 per 100,000 person-years. An increase in the admission rate in the 8-16 weeks age group (RR 1.46, 95% CI 1.12-1.91), those receiving vaccination, was compensated for by decreases in the 17-24 weeks (RR 0.77, 0.63-0.94), 25-32 weeks (RR 0.71, 0.59-0.86) and 41-52 weeks (RR 0.80, 0.66-0.98) age groups. Using interrupted time series analysis, we observed a significant decrease in incidence in the 0-12 months age group (RR 0.80, 0.67-

0.96), but not in the overall 0-36 months age group (RR 1.09, 0.98-1.20). There was no significant change in the proportion of children requiring surgical intervention or with major complications of intussusception. Length of hospital stay decreased among infants receiving surgery for intussusception.

Conclusions

Our results suggest that introduction of rotavirus vaccination in England has resulted in a downward shift in the age at which intussusception occurs in infants, with no overall increase in hospital admission rate or disease severity. These findings support the view that the benefits of rotavirus vaccination outweigh the small increased risk of intussusception in the early post-vaccination period.

56

57 INTRODUCTION

58

59 Rotavirus infection was previously a major cause of general practice consultations,
60 emergency department presentations and hospital admissions for acute gastroenteritis in
61 England and Wales and resulted in annual health service costs in excess of £14 million [1]. In
62 resource-poor countries, it has been an important cause of childhood mortality, influencing
63 the drive to develop a vaccine [2].

64 The first rotavirus vaccine, RotaShield® (Wyeth Lederle Vaccines), was introduced into the
65 United States immunization programme in 1998 but was withdrawn from the market when
66 it was unexpectedly found to be associated with an increased risk of intussusception in the
67 early post-vaccination period [3]. However, it was noted that the overall incidence of
68 intussusception in children did not rise significantly following introduction of RotaShield
69 vaccination and appeared to be reduced among infants aged 5-6 months, leading to the
70 hypothesis that vaccination precipitated earlier onset of intussusception in predisposed
71 children [4].

72 The subsequent development of two other live oral vaccines, Rotarix® (RV1;
73 GlaxoSmithKline) and RotaTeq® (RV5; Merck & Co), monovalent and pentavalent vaccines
74 respectively, involved large prelicensure randomised controlled safety trials powered to
75 detect a signal for this unexpected and unexplained adverse effect [5], [6]. Neither study
76 identified an increased risk of intussusception among infants receiving these vaccines. In
77 2009, the World Health Organisation (WHO) recommended that rotavirus vaccination for

78 infants should be included in all national immunisation programmes [7]. Nevertheless, given
79 that the background incidence of intussusception increases with age during early infancy,
80 strict upper limits were placed on the age at which vaccine doses can be given, with the
81 WHO recommending that all doses should be completed by 32 weeks of age [7].

82 RV1 was introduced into England's immunisation programme in July 2013, as a two-dose
83 schedule at 8 and 12 weeks of age (Table 1). Uptake of the vaccine rapidly rose to a
84 nationwide average of 93.3% for one dose and 88.3% for two doses in the first cohort to be
85 offered vaccination [8]. The vaccine has been highly effective in reducing laboratory-
86 confirmed rotavirus infections in England [9], [10].

87 Post-licensure surveillance has continued to monitor the risk of intussusception among
88 infants receiving vaccination with RV1 or RV5. Self-controlled case series analyses
89 conducted in England, the USA, Australia, Singapore, Brazil and Mexico have all identified an
90 increased risk of intussusception in the seven-day period following the first and/or second
91 dose of RV1 [11], [12], [13], [14], [15].

92 A study conducted by Public Health England demonstrated an increased risk of
93 intussusception following the first dose of RV1 and predicted that introduction of
94 vaccination would result in around 21 additional admissions for intussusception per annum
95 in England, but that this would be outweighed by the benefits of vaccination [11].

96 Despite this elevated risk, data from ecological analyses suggests that longer term
97 hospitalization rates for intussusception have not increased following introduction of RV1
98 and RV5 [16], [17], [18], [19], [20].

The primary aim of this retrospective ecological study was to investigate whether there has been an overall change in the rate of hospital admissions for intussusception in the paediatric population in England following introduction of rotavirus vaccination. Secondary aims were to investigate whether the age-specific hospital admission rate, proportion of children developing complications of intussusception or its management, or average length of hospital stay have changed following vaccine introduction.

METHODS

Data Sources

Hospital Episode Statistics (HES) data are recorded for all individuals admitted to National Health System hospitals in England and code for admission, demographic, diagnostic and procedural details. HES data is routinely reported for each fiscal year spanning the period 1st April to 31st March. We obtained HES data for all children aged less than 3 years with a recorded *International Statistical Classification of Diseases and Related Health Problems, 10th revision* (ICD-10) diagnostic code for intussusception (K56.1) or *Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4.7* (OPCS 4.7) code for a surgical or radiological intervention to address intussusception (full list available in Supplementary File 1) in any position, between the years 2008/09 and 2017/18 inclusive. It has been demonstrated previously that HES data capture the majority of hospital admissions for intussusception, with agreement between cases identified in HES data and

cases identified in a prospective surveillance study employing Brighton Collaboration case definition criteria [21]. Duplicate entries were excluded and only the first recorded admission including the intussusception diagnostic code for an individual was included, possible due to the existence of unique individual patient identifiers within the HES dataset. We also searched for ICD-10 diagnostic codes for complications of intussusception or its management (full list available in Supplementary File 1).

Hospital admission rates, equivalent to crude incidence rates, were calculated using annual England mid-year population estimates for individual year groups obtained from the Office for National Statistics, which can be taken to represent the number of person-years for all individuals in the specified age group across the corresponding one-year period [22]. The figures for each calendar year were assumed to be equivalent for the corresponding fiscal year. Births were assumed to be evenly distributed throughout the year. All admission rate figures are reported per 100,000 person-years.

Data Analysis

We examined demographic data, surgical rates, clinical outcomes, and length of hospital stay for individuals admitted with intussusception.

Rate ratios (RR) and corresponding 95% confidence intervals and P-values were computed using modified Poisson regression analysis [23]. The rate of intussusception admissions during the years following introduction of the rotavirus vaccine (2014/15 - 2017/18) was

compared to the rate of admissions during the years preceding vaccine introduction (2008/09 - 2012/13).

Primary comparisons were performed in children under 1 year of age.

The majority of children in the United Kingdom correctly receive their first set of routine primary immunisations, which include RV1, between 8-12 weeks of age and their second set of immunisations between 12-16 weeks of age [24]. We therefore decided to additionally examine changes in the rate of intussusception admissions among infants aged 8-16 weeks, representing the majority of infants who would be completing the full vaccination course.

Preliminary analyses confirmed that attempts to use smaller 8-12 week and 13-16 subgroups, corresponding to infants receiving the first and second vaccine doses respectively, resulted in estimates with poor precision. As well as the overall 0-12 months age group, sub-comparisons were therefore performed for the 8-16 weeks age group and for similar sized comparator groups aged 17-24 weeks, 25-32 weeks, 33-40 weeks and 41-52 weeks.

Secondary comparisons were then performed for the age groups 13-24 months, 25-36 months and 0-36 months.

A sensitivity analysis was performed to evaluate whether overall changes in hospital admission rates in the 0-12 months and 0-36 months age groups observed over the study period were significant taking into account the pre-existing baseline trend in the hospital admission rate for intussusception in England [21]. We performed an interrupted time series analysis using a step-change model with Poisson regression, with 2014/15 as the interruption point. Overdispersion was assessed using residual plots and the Kolmogorov-Smirnov test. Autocorrelation was assessed using autocorrelation plots.

166

167 The proportions of intussusception cases that required surgical intervention or developed
168 complications of intussusception in the pre-vaccine and post-vaccine periods were
169 compared using the Chi-squared test. Length of stay in the pre-vaccine and post-vaccine
170 periods was compared using the Wilcoxon rank-sum test.

171

172 The year of vaccine introduction, 2013/14, was excluded from the above analyses, given the
173 transition from unvaccinated to vaccinated individuals that took place during that year.

174

175 Statistical analysis was carried out using R version 3.6.1 (R Foundation for Statistical
176 Computing, Vienna, Austria).

177

178 As an analysis of non-identifiable routinely collected data, following HRA guidance
179 (<http://www.hra-decisiontools.org.uk/ethics/>), our study did not require ethical review.

180

181 **RESULTS**

182

183 The total person-time of follow-up for children under 3 years of age across the ten-year
184 study period equated to 20,143,062 person-years. Cumulative mid-year population
185 estimates for England across this same period were 6,704,501 for children aged 0-12

months, 6,725,215 for children aged 13-24 months, and 6,713,346 children for aged 25-36 months.

After excluding duplicate data and filtering for the first admission for each individual that included the diagnostic code for intussusception, HES data held 3026 admission records including the diagnostic code for intussusception in children aged 0-36 months during the ten-year period (admission rate 15.0 per 100,000), 2112 (69.8%) of which were in those aged 0-12 months (31.5 per 100,000) (Table 2). 2847 (94.1%) children had the intussusception diagnostic code in the first position. Searching only by ICD-10 diagnostic code identified 98.0% of children with either an ICD-10 diagnostic code or OPCS 4.7 procedure code for intussusception in any position (3088 individuals).

The peak rate of intussusception admissions among children aged 0-36 months was seen in the 25-32 weeks age group (44.6 per 100,000). Intussusception was seen more commonly in males (64.5%). This finding was consistent between the pre-vaccine (64.2%) and post-vaccine (63.7%) periods. Median age at the time of admission for intussusception was 37 weeks overall and was higher in males (38 weeks) than in females (35 weeks). 730 (24.1%) individuals had a recorded OPCS 4.7 code for a surgical intervention to address intussusception. Median length of hospital admission was 1-2 days irrespective of age or sex, but was longer (4 days) among children with a recorded OPCS 4.7 code for a surgical intervention to address intussusception.

For the 0-12 months age group as a whole, there was a significant decrease in the rate of intussusception admissions for the post-vaccine period relative to the pre-vaccine period (RR 0.86, 95% CI 0.78-0.94) (Table 3). This finding remained significant when taking into account the pre-existing baseline trend in admission rates for intussusception using interrupted time series analysis (RR 0.80, 0.67-0.96) (Figure 1).

Restricting our analysis to infants aged 8-16 weeks, there was a significant increase in admission rate in the post-vaccine period (RR 1.46, 1.12-1.91). Further sub-analysing this group, there was a significant relative rate increase in those aged 8-12 weeks (RR 1.83, 1.17-2.88), corresponding to individuals receiving the first vaccine dose, but not in the age group 13-16 weeks (RR 1.29, 0.93-1.80), corresponding to those receiving the second dose. In contrast, there was a significant decrease in admission rate in the post-vaccine period for the 17-24 weeks age group (RR 0.77, 0.63-0.94), the 25-32 weeks age group (RR 0.71, 0.59-0.86), and the 41-52 weeks age group (RR 0.80, 0.66-0.98). In the 33-40 weeks age group, there was no significant change in admission rate for the post-vaccine period relative to the pre-vaccine period (RR 0.94, 0.76-1.15). Annualised admission rates for each of these subgroups over the ten-year study period are illustrated in Figure 2.

In the secondary analyses, no change in the hospital admission rate for intussusception was seen in either the 13-24 months (RR 0.96, 0.81-1.13) or the 25-36 months (RR 0.96, 0.75-1.23) age groups. A reduction in admission rate was observed in the 0-36 months age group (RR 0.86, 0.80-0.93), which was not significant when accounting for the pre-existing baseline trend in our sensitivity analysis (RR 1.09, 0.98-1.20).

Table 4 demonstrates that the percentage of children with intussusception in the 41-52 weeks age group who had a recorded OPCS 4.7 procedure code for a surgical intervention to address intussusception was lower in the post-vaccine period (17.5%) than in the pre-vaccine period (26.8%). There were no other differences between the two time periods in the percentage of intussusception cases with a recorded surgical intervention, either among the 0-36 months age group as a whole or among other age subgroups. There were no identifiable differences in the proportion of children developing any of several important complications of intussusception between the two time periods.

Table 5 demonstrates length of stay for each of the age subgroups included in the study across the study period. Length of stay fell from the pre-vaccine period to the post-vaccine period among infants aged 0-12 months with a recorded surgical intervention to address intussusception.

DISCUSSION

In this retrospective ecological study, we sought to determine whether the introduction of universal RV1 rotavirus vaccination for infants in England at 8 weeks and 12 weeks of age was associated with a change in the rate of intussusception hospital admissions in the paediatric population.

249 We identified a hospital admission rate for intussusception in the 0-12 months age group in
250 England of 31.5 per 100,000 across the ten-year period 2008/09 – 2017/18, with annual
251 admission rates ranging from 25.0 per 100,000 to 35.2 per 100,000.

252 This admission rate figure compares with European estimates of incidence rates of
253 intussusception in infants aged under 1 year of 13.0 per 100,000 in Finland, 37.5 per
254 100,000 in France, 60.2 per 100,000 in Germany (26.6 per 100,000 before correcting for
255 underreporting), 40.0 per 100,000 in Iceland, 39.0 per 100,000 in Italy, 27.9 per 100,000 in
256 the Netherlands, 37.1 per 100,000 in Norway, 38.0 per 100,000 in Switzerland, and a value
257 of 40.6 per 100,000 for Europe overall [25], [26], [27], [28], [29], [30], [31], [32], [33]. The
258 rate of intussusception observed in infants in England is at the lower end of the range of
259 mean annual incidence rates reported internationally (3.8 per 100,000 - 380.2 per 100,000)
260 [33]. Differences in observed rates of intussusception both within and between countries
261 and regions may reflect a combination of differing disease definitions or coding systems as
262 well as real differences in the incidence of intussusception. The latter may be driven by
263 genetic or environmental factors, including dietary patterns and levels of exposure to
264 infectious agents [34].

265 The observed peak in cases of intussusception in infants aged 4-7 months is in keeping with
266 the findings of other studies conducted in Europe, as well as the age distribution of
267 intussusception across other regions internationally [26], [29], [31], [33], [35]. The median
268 age at admission with intussusception among children aged 0-36 months identified in our
269 study was 37 weeks (IQR 25-59 weeks). This is similar to figures previously reported for
270 England as well as for Denmark, Finland, Iceland and Switzerland but lower than the median
271 age at admission seen in France, Germany, Italy and Europe as a whole (47 weeks) [33].

272

273 In keeping with previous work showing an early increase in risk of intussusception after
274 vaccination in a number of different populations [11], [12], [13], [14], [15], our results
275 suggest that there is an increase in the rate of intussusception hospital admissions in
276 England among children aged 8-16 weeks.

277 Resembling findings from a number of other post-licensure ecological studies [4], [16], [17],
278 [18], [19], [20], we found that there was a reduction in the rate of intussusception hospital
279 admissions in the 0-12 months and 0-36 months age groups, which remained significant for
280 infants but not for the 0-36 months age group as a whole after accounting for the pre-
281 existing baseline temporal trend.

282 Although there was a rise in admission rate in the 8-16 weeks age group, this was
283 compensated for by a reduction in admission rate among older age groups (17-24 weeks,
284 25-32 weeks and 41-52 weeks), despite intussusception being more common in these age
285 groups overall. Our findings are consistent with those reported in the United States, which
286 similarly suggest that introduction of rotavirus vaccination has resulted in a downward shift
287 in the age distribution of childhood intussusception, with no increased overall risk [4], [16],
288 [36]. An analysis conducted following withdrawal of the RotaShield vaccine demonstrated
289 an increase in intussusception cases among those aged 2-4 months following vaccine
290 introduction, but a reduction in rates of intussusception in the 5-6 months age group [4]. A
291 reappraisal of data from that study demonstrated that the increase in risk of intussusception
292 in the immediate 3 weeks post-vaccination was followed by a decrease in relative risk in
293 subsequent postvaccination weeks [36]. A more recent study showed that the rate of
294 intussusception in infants aged 6-14 weeks receiving vaccination with RV1 or RV5 has been

higher in all years versus the pre-vaccine baseline, with this increase being statistically significant in all but two years and apparently driven by an increase in incidence among those aged 8-11 weeks who had received the first vaccination dose, but without a corresponding reduction in the rate of intussusception in the 15-24 week or 25-34 week age groups [16]. That study demonstrated that the overall rate of intussusception among infants in the USA has decreased non-significantly following rotavirus vaccine introduction, whilst a subsequent longitudinal cohort revealed that risk among children followed up to two years of age has not increased [37]. In the context of an increase in risk in the immediate post-vaccination period, these findings would suggest that the rate of intussusception would likely have decreased among older infant age groups in the USA. A population-based study conducted in the Taiwanese population identified a significant reduction in the rate of intussusception in the 25-34 weeks age group following introduction of rotavirus vaccination, but did not identify an increase in risk of intussusception in the 6-14 weeks age group receiving the vaccination series [19]. However, the authors of that study acknowledged that their ability to identify a small increase in the rate of intussusception admissions among children receiving vaccination was limited by the relatively small Taiwanese birth cohort together with low vaccine uptake during the study period.

It is notable that a compensatory reduction in cases of intussusception in older infants could lead to violation of a key assumption of the self-controlled case series methodology, namely that the incidence of intussusception in the control period would be unchanged from the pre-vaccine baseline [38]. This approach, which has been used in numerous studies demonstrating an increase in risk of intussusception in the immediate post-vaccination period, might therefore provide falsely elevated risk estimates. This could explain why we

have not identified the increase in cases of intussusception that was predicted to arise following introduction of rotavirus vaccination in England [11].

Two key hypotheses have been proposed for the mechanism by which introduction of rotavirus vaccination might result in the offsetting of an initial early increase in risk of intussusception post-vaccination by a fall in incidence among older children.

Firstly, it has been suggested that the vaccine might induce intussusception in already-susceptible children, who would otherwise have developed intussusception at a later timepoint during infancy [4]. This mechanism would be in keeping with the observation in this and previous studies that the compensatory decrease in cases of intussusception appears to closely follow the elevated risk period associated with vaccination [4], [36], as well as the fact that this trend persists even when circulating rotavirus levels are low. However, this hypothesis would not explain suggestions herein and elsewhere that the overall rate of intussusception in infants may have declined below the pre-vaccination baseline [4], [16], [19].

Secondly, rotavirus vaccination might reduce cases of intussusception attributable to wild-type rotavirus infection in older infants. This mechanism, unlike the first, could account for a reduction in overall cases of intussusception in infants following vaccine introduction. However, this hypothesis rests on the unproven assumption that wild-type rotavirus can trigger intussusception. A previous case series demonstrated that faecal samples from patients with intussusception displayed electron microscopic evidence of rotavirus infection in 37% cases [39]. Furthermore, it has been shown that acute rotavirus gastroenteritis is associated with an increase in ileal wall thickness and in the size and number of mesenteric

lymph nodes [40]. Conversely, other investigators have failed to identify evidence in support of an aetiological role for rotavirus in intussusception and point to the fact that intussusception does not universally demonstrate the seasonality that might be expected if rates were to be measurably influenced by rotavirus infection in children [41], [42]. Additionally, this hypothesis would suggest that the compensatory reduction in cases would only occur during time periods in which wild-type rotavirus is circulating.

It is possible that these two mechanisms could co-exist. In either scenario, the actual pathological mechanism by which receipt of the vaccine might result in intussusception remains unknown. It has been suggested that the vaccine might induce hyperplasia or hypertrophy of gut-associated lymphoid tissue, providing a lead point for intussusception, though this finding was not borne out in a previous study [43]. A further study failed to find evidence of the presence of the vaccine strain of rotavirus within the ileal tissue or lymphoid tissue of pathological specimens from children who had received the RotaShield vaccine and developed intussusception [44].

Our results demonstrate that there has not been a significant change in the need for surgical intervention, development of several clinical complications or overall length of stay among infants admitted with intussusception, which would suggest that the severity of disease has not increased following introduction of rotavirus vaccination.

Existing evidence suggests that the benefits of rotavirus vaccination in reducing morbidity associated with rotavirus admissions outweigh the reasonably small increased absolute risk

of intussusception observed in the early post-vaccination period [45]. Our findings add weight to this notion by suggesting that overall childhood admissions for intussusception have not increased following introduction of universal RV1 rotavirus vaccination with high population coverage. An increase in the rate of intussusception hospital admissions among infants in the immediate post-vaccination period has been compensated for by a reduction in the admission rate among older infant age groups. There has been no overall change in rates of surgery or deleterious clinical outcomes for children aged under 3 years admitted with intussusception. Furthermore, median length of hospital stay remains unchanged overall following vaccine introduction and has fallen among patients undergoing surgery within the age group receiving vaccination.

A major strength of this study is the use of the HES dataset, which represents the entire population of England. Using this dataset, we were able to examine temporal changes in clinical outcomes associated with intussusception, including in length of hospital stay. However, whilst ICD-10 diagnostic coding for intussusception captures the majority of intussusception hospital admissions [21], the fact that only 39.6% individuals had a recorded OPCS 4.7 code for a surgical or radiological intervention to address intussusception would suggest that HES does not have complete data capture for these interventions. A previous audit of intussusception cases in the UK and Ireland suggested that therapeutic enema reduction was attempted in 92% infants and surgical intervention was required in 42.5% infants [46]. It is also unclear whether the HES dataset provides reliable data capture for clinical complications of intussusception, though it is perhaps unlikely that coding for these complications would have changed materially over time.

386 Another limitation of this study was an inability to perform subgroup analysis within the 0-
387 12 months age group using the interrupted time series analysis design. Despite including the
388 entire infant population of England over a ten-year period, the rarity of intussusception as
389 an event meant that power and precision were unacceptably poor when attempting to
390 apply this methodology to subgroups. Nonetheless, the primary analysis method employed
391 is consistent with the methodology used in previous studies [16], [19], [20].

392 A third limitation is the lack of data on individual-level vaccine status, which is not routinely
393 available within the HES dataset. We were consequently unable to identify the minority of
394 individuals who did not receive vaccination in the period 2014/15 - 2017/18, ascertain the
395 precise timing of vaccination of individual cases, or estimate the interval between receipt of
396 vaccination and onset of intussusception.

397 We note that two other changes took place to England's routine childhood vaccination
398 schedule in 2013, the same year as rotavirus vaccination was introduced, as shown in Table
399 1. Meningitis C vaccination at 4 months of age was discontinued in June 2013, whilst there
400 was a phased introduction of the annual live attenuated influenza vaccination for children
401 aged 2 years and above from September 2013. There were also several other changes to the
402 vaccination schedule during the course of the ten-year study period. Though none of the
403 vaccines that were removed from or added to the schedule during the study period have
404 previously been linked to intussusception risk in children, we cannot exclude the effect of
405 other changes to the vaccination programme as an unmeasured confounder in this study.

406 Private emergency department care is not available in England, with the majority of private
407 healthcare services focusing on provision of elective medical care [47]. This means that it is
408 unlikely that children presenting with intussusception during the study period would have

409 been managed outside of the NHS. However, whilst there is relatively little private
410 healthcare expenditure on children generally in the United Kingdom [47], there is a paucity
411 of publicly available information providing detailed figures or statistics on private healthcare
412 provision. Consequently, the possibility that some cases of intussusception were managed in
413 private settings and therefore not recorded within the HES dataset cannot be excluded,
414 representing a further theoretical limitation of this study.

415 Internationally, there has been a shift towards ambulatory management of intussusception
416 in the emergency department setting following successful radiological reduction, without
417 admission to hospital [48]. If this were the case in England, HES data would underestimate
418 the true incidence of intussusception. However, clinical guidelines concerning paediatric
419 intussusception in England recommend hospital admission for 24-48 hours following
420 successful enema reduction [49]. It is notable that recurrence rates of intussusception
421 following enema reduction are higher in England than in North America, which may account
422 for a lack of shift towards ambulatory care protocols in England [50].

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Authors' contributions:

RM developed the idea and design of the study. LM 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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587

588 Table 1: Routine childhood vaccination schedule for England correct at 31st March 2018 for children
 589 up to 8 years of age.

Diseases Protected Against	Vaccine Given	Changes to Vaccination Schedule*
2 months		
Diphtheria, Tetanus, Pertussis, Polio, Haemophilus influenzae type b, Hepatitis B	6-in-1 vaccine: DTaP/IPV/Hib/HepB	Hepatitis B vaccine added to 5-in-1 vaccine in August 2017
Rotavirus Gastroenteritis	Rotavirus	Introduced July 2013
Meningococcal group B	MenB	Introduced September 2015
Pneumococcal (13 serotypes)	Pneumococcal Conjugate Vaccine (PCV)	Change from 7-serotype PCV7 vaccine to 13-serotype PCV13 vaccine in April 2010
3 months		
Diphtheria, Tetanus, Pertussis, Polio, Haemophilus influenzae type b, Hepatitis B	6-in-1 vaccine: DTaP/IPV/Hib/HepB	Meningitis C vaccine dose at 3 months removed in July 2016 Hepatitis B vaccine added to 5-in-1 vaccine in August 2017
Rotavirus Gastroenteritis	Rotavirus	Introduced July 2013
4 months		
Diphtheria, Tetanus, Pertussis, Polio, Haemophilus influenzae type b, Hepatitis B	6-in-1 vaccine: DTaP/IPV/Hib/HepB	Meningitis C vaccine dose at 4 months removed in June 2013 Hepatitis B vaccine added to 5-in-1 vaccine in August 2017
Meningitis B	MenB	Introduced September 2015
Pneumococcal (13 serotypes)	PCV	Change from 7-serotype PCV7 to 13-serotype PCV13 vaccine in April 2010
12-13 months		
Hib/Meningitis C	Hib/MenC	
Measles, Mumps, Rubella	MMR	
Pneumococcal (13 serotypes)	PCV Booster	Change from 7-serotype PCV7 to 13-serotype PCV13 vaccine in April 2010

Meningitis B	MenB Booster	Introduced September 2015
2 – 8 years (annually)		
Influenza	Live attenuated influenza vaccine (LAIV)	Phased introduction from September 2013
3 years 4 months		
Measles, Mumps, Rubella	MMR	
Diphtheria, Tetanus, Pertussis, Polio	4-in-1 vaccine booster: DTaP/IPV	

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591 *Changes shown are for the ten-year study period 1st April 2008 – 31st March 2018.

592

593 Table 2: Age and sex breakdown, interventions and median length of stay among children aged 0-36
594 months admitted to hospitals in England with intussusception during the period 2008/09 – 2017/18.

	n	%	Mean Admission Rate (per 100,000)	Median Age in Weeks (IQR)	Median Length of Stay in Days (IQR)
Age					
0-36 months	3026	100.0	15.0	37 (25-59)	1 (1-3)
0-12 months	2112	69.8	31.5	-	1 (1-3)
<8 weeks	32	1.1	3.0	-	1 (0-3.25)
8-16 weeks	239	7.9	21.4	-	2 (1-4)
8-12 weeks	87	2.9	15.6	-	2 (1-4)
13-16 weeks	152	5.0	27.3	-	2 (1-4)
17-24 weeks	459	15.2	41.0	-	2 (1-3)
25-32 weeks	499	16.5	44.6	-	1 (1-3)
33-40 weeks	426	14.1	38.1	-	1 (1-3)
41-52 weeks	457	15.1	27.2	-	1 (1-2)
13-24 months	621	20.5	9.2	-	1 (1-2)
25-36 months	293	9.7	4.4	-	1 (1-3)
Sex					
Male	1953	64.5	18.9	38 (25-61)	1 (1-3)
Female	1073	35.5	10.9	35 (23-56)	1 (1-3)
Intervention					
Surgical	730	24.1	3.6	35 (23-51.75)	4 (3-5)
Radiological	576	19.0	2.9	38 (26-59)	2 (1-2)
Both	109	3.6	0.5	37 (22-54)	3 (2-5)
Missing	1829	60.4	9.1	-	-

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596 Percentages may not add to 100% owing to rounding.

597 Abbreviations: IQR, Interquartile Range.

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599 Table 3: Number of annual hospital admissions, admission rate per 100,000 person-years and rate ratio (RR) for intussusception in the pre-vaccine (2008/09
600 - 2012/13) and post-vaccine (2014/15 - 2017/18) periods.

601

Age Group	2008/09 – 2012/13		2014/15 – 2017/18		RR (95% CI)	P-value
	n	Mean rate (range)	n	Mean rate (range)		
0-12 months	1135	33.6 (32.2-35.2)	758	28.6 (25.0-31.7)	0.86 (0.78-0.94)	0.0013
8-16 weeks	100	17.8 (14.1-20.5)	116	26.3 (17.2-30.8)	1.46 (1.12-1.91)	0.0051
8-12 weeks	32	11.4 (5.4-16.1)	46	20.8 (10.8-26.9)	1.83 (1.17-2.88)	0.0085
13-16 weeks	68	24.2 (19.4-30.8)	70	31.7 (23.5-36.2)	1.29 (0.93-1.80)	0.13
17-24 weeks	252	44.7 (42.0-50.0)	152	34.4 (29.0-38.6)	0.77 (0.63-0.94)	0.012
25-32 weeks	288	51.2 (41.5-65.2)	161	36.5 (28.9-42.1)	0.71 (0.59-0.86)	0.00058
33-40 weeks	219	38.9 (36.2-40.7)	161	36.4 (29.4-41.2)	0.94 (0.76-1.15)	0.53
41-52 weeks	254	30.1 (27.8-33.6)	160	24.2 (19.9-26.9)	0.80 (0.66-0.98)	0.030
13-24 months	317	9.5 (8.1-11.8)	246	9.1 (8.4-9.4)	0.96 (0.81-1.13)	0.59
25-36 months	145	4.4 (3.7-5.1)	116	4.2 (3.9-4.7)	0.96 (0.75-1.23)	0.75
0-36 months	1597	16.0 (15.8-16.4)	1120	13.8 (12.8-15.0)	0.86 (0.80-0.93)	0.00019

602 Table 4: Number and percentage of intussusception cases requiring surgery or developing clinical
603 complications during the pre-vaccine (2008/09 - 2012/13) and post-vaccine (2014/15 - 2017/18)
604 periods.

Outcome	2008/09 – 2012/13		2014/15 – 2017/18		P-value
	n	%	n	%	
Surgery	400	25.1	255	22.8	0.17
0-12 months	307	27.0	185	24.4	0.20
8-16 weeks	30	30.0	37	31.9	0.76
8-12 weeks	14	43.8	15	32.6	0.32
13-16 weeks	16	23.5	22	31.4	0.30
17-24 weeks	66	26.2	37	24.3	0.68
25-32 weeks	74	25.7	38	23.6	0.62
33-40 weeks	64	29.2	45	28.0	0.79
41-52 weeks	68	26.8	28	17.5	0.030
13-24 months	59	18.7	51	20.8	0.53
25-36 months	34	23.5	19	16.4	0.16
Ischaemia / Infarction	17	1.1	21	1.9	0.11
Perforation	21	1.3	17	1.5	0.80
Peritonitis	7	0.4	3	0.3	0.68
Surgical Puncture	14	0.9	12	1.1	0.77

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606 Table 5: Median length of stay for all intussusception cases and surgical cases in the pre-vaccine (2008/09 - 2012/13) and post-vaccine (2014/15-2017/18)
607 periods.

Age Group	All Cases			Surgical Cases		
	Median Length of Stay in Days (IQR)		P-value	Median Length of Stay in Days (IQR)		P-value
	2008/09 – 2012/13	2014/15 – 2017/18		2008/09 – 2012/13	2014/15 – 2017/18	
0-12 months	1 (1-3)	1 (1-3)	0.61	4 (3-6)	3.5 (3-5)	0.035
8-16 weeks	1 (1-4)	2 (1-4)	0.099	6 (4-8)	4 (3-5)	0.0035
8-12 weeks	1 (0.75-7)	2 (1-3)	0.70	7 (4-9.5)	3 (2-5)	0.021
13-16 weeks	1 (1-3)	2 (1-4)	0.081	5 (4-6.5)	4 (3-5)	0.098
17-24 weeks	1 (1-3)	2 (1-3)	0.94	4 (3-6)	3.5 (2.75-5)	0.22
25-32 weeks	1 (1-3)	1 (1-3)	0.52	4 (3-5)	3 (3-5)	0.41
33-40 weeks	2 (1-3)	1 (1-3)	0.10	4 (3-5)	4 (3-5)	0.64
41-52 weeks	1 (1-2.75)	1 (1-2)	0.44	3 (2-5.25)	3 (2-5)	0.68
13-24 months	1 (1-2)	1 (1-3)	0.19	3 (2-5)	4 (2-5)	0.46
25-36 months	1 (0-1)	1 (0.75-4)	0.78	4 (3-5)	4 (4-5)	0.23
0-36 months	1 (1-3)	1 (1-3)	0.85	4 (3-6)	4 (3-5)	0.23

Figure 1: Time trend in intussusception admission rate per 100,000 person-years in the 0-12 months age group in England between 2008/09 - 2017/18 inclusive, excluding the year 2013/14, modelled for observed trend following rotavirus vaccination introduction (solid line) and predicted trend for counterfactual scenario where vaccination was not introduced (dashed line). Actual admission rates for each year shown as blue circles. RR refers to rate ratio computed using interrupted time series analysis with a level change at 2014/15, excluding the year 2013/14, with 95% confidence intervals included in brackets. Shaded area represents post-vaccine period.

Figure 2: Trend in intussusception admission rate per 100,000 person-years in age subgroups 8-16 weeks, 17-24 weeks, 25-32 weeks, 33-40 weeks and 41-52 weeks between financial years 2008/09 - 2017/18 inclusive in England. Error bars indicate 95% confidence intervals for admission rate estimates. RR refers to rate ratio computed for the combined post-vaccine period compared to the combined pre-vaccine period using modified Poisson regression, excluding the year 2013/14, with 95% confidence intervals included in brackets. Shaded area represents fiscal year 2013/14 during which rotavirus vaccination was introduced.

627 Supplementary data

628 # OPCS 4.7 SURGICAL PROCEDURE CODES

629

630 G33.4 Open reduction of intussusception of gastroenterostomy

631 G69 Excision of ileum

632 G70 Open extirpation of lesion of ileum

633 G71 Bypass of ileum

634 G72 Other connection of ileum

635 G74 Creation of artificial opening into ileum

636 G76 Intra-abdominal manipulation of ileum

637 G78 Other open operations on ileum

638 H01 Emergency excision of appendix

639 H02 Other excision of appendix

640 H03 Other operations on appendix

641 H06 Extended excision of right hemicolon

642 H07 Other excision of right hemicolon

643 H11 Other excision of colon

644 H17 Intra-abdominal manipulation of colon

645 H46 Other operations on rectum

646 T30 Opening of abdomen

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659 # OPCS 4.7 RADIOLOGICAL PROCEDURE CODES

660

661 H30.1 Radiological reduction of intussusception of colon using barium enema

662 H46.1 Radiological reduction of intussusception of rectum using barium enema

663 H46.2 Hydrostatic reduction of intussusception of rectum

664 G82.1 Radiological reduction of intussusception of ileum using barium enema

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690 # ICD-10 DIAGNOSTIC CODES FOR CLINICAL COMPLICATIONS

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692 K63.1 Perforation of intestine (nontraumatic)

693 K55 Vascular disorders of intestine (includes ischaemia, necrosis)

694 K65 Peritonitis

695 T81 Complications of procedures, not elsewhere classified

696 T88 Other complications of surgical and medical care, not elsewhere classified

697 Z48 Other surgical follow-up care

698 Z98.0 Intestinal bypass and anastomosis status

699

700