Original Contribution

Oral Polio Vaccine and Intussusception: A Data Linkage Study using Records for Vaccination and Hospitalization

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The authors investigated the possibility of an association between oral polio vaccine (OPV) and intussusception by linking Scottish vaccination and hospitalization data sets and performing self-controlled case series analysis. The issue was important because rotavirus vaccine, another live oral virus vaccine, was withdrawn from the market in 1999 after studies showed a strong association with intussusception. OPV was recommended for all infants in the United Kingdom at ages 2, 3, and 4 months until 2004, when new combination vaccines containing inactivated poliovirus were introduced. Analysis was carried out for 466 intussusception cases occurring in 1987–1999 for which linked records on OPV vaccination were available. Six possible risk periods for intussusception, ranging from 3 days after vaccination to 41 days after vaccination, were examined, with separate analysis for each of the three OPV doses and also for data on all three doses combined. Of the 24 possible risk periods examined, the relative incidence of intussusception after vaccination was unchanged for 18, significantly decreased for five, and significantly increased for only one. The authors conclude that overall, there is no evidence for an association between OPV and intussusception, even when each dose is considered separately.

intussusception; medical record linkage; poliovirus vaccines

Abbreviations: CI, confidence interval; OPV, oral polio vaccine; RI, relative incidence; SCCS, self-controlled case series.
a second dose scheduled for age 4 months (5) and 14–27 days after a third dose scheduled for age 4 months (6). Therefore, we considered our study to be a useful additional piece of evidence in interpreting these already published findings.

MATERIALS AND METHODS
Hospitalization records
All nonobstetric and nonpsychiatric general and acute inpatient discharges from National Health Service hospitals in Scotland are recorded within one defined data set. This data set captures all pediatric hospitalizations and includes information on patient characteristics, demographic factors, episode management, and general clinical measures. The records are routinely collected from all National Health Service hospitals, and their accuracy and completeness are validated by comparison of an annual sample of information with clinical notes (10). For this study, records of hospitalizations with a code for intussusception (International Classification of Diseases, Ninth Revision, code 560.0 or International Classification of Diseases, Tenth Revision, code K56.1) in any of the six diagnostic positions were extracted for the years 1987–1999.

Vaccination records
Children are automatically entered into the Standard Immunisation and Recall System at birth or upon migration. During the study period, the system covered 90 percent of the population of Scotland. Three areas (Grampian, Orkney, and Shetland) operated a different scheme and were unavailable to provide data for the study. Therefore, the number of vaccination records available approximated 90 percent of the national birth cohort. The records include information on history of OPV vaccination by date, for all doses; the patient’s surname, forename, date of birth, sex, and Community Health Index number (a unique identifier); and home postcode. A number of measures are in place to ensure as high a degree of data completeness and accuracy as possible, including the requirement to enter the Community Health Index number to access the records, age-specific prompts for data entry, and incentive payments. Data that are clinically impossible will not be accepted by the system.

Only records with validated vaccination dates were used in the analysis; records with incomplete dates for vaccination were excluded. Records were obtained for all children for the years 1987–1999. The annual birth cohort for this period ranged from 55,147 (1999) to 67,024 (1991).

Record linkage
To allow for imperfections in both vaccination and hospitalization records due to occasional discrepancies in the recording of personal information, the “probability matching” method was used to bring the two data sets together. This method—estimated to be 13–14 percent more accurate than “exact matching” (11)—involves comparing patients’ surnames, forenames, sexes, dates of birth, and home postcodes from both data sets. The linkage method has been designed to extract the maximum amount of discrimination from the available identifying information, with an estimated accuracy of 98 percent (11). The resulting linked file enabled analysis of each patient’s hospitalizations following vaccination. Only case children who had received three doses of OPV were included in the final analysis, because if fewer than three doses had been recorded, we could not ascertain which dose had been omitted. Cases were also excluded if the interval between OPV doses was less than 28 days.

Analysis
The linked data were analyzed using the self-controlled case series (SCCS) method, which has been developed to analyze clinical events in vaccinated persons (12, 13). It enables one to calculate the relative incidence of disease for various risk periods after vaccination, adjusting for possible age effects (14). In our study, we controlled for age monthly and restricted the analysis to children who were under age 1 year at admission. The SCCS method is recognized as being more powerful than a case-control study and less subject to bias and confounding factors because of the cases’ acting as their own controls, using data from outside the risk period (12, 13).

Initial suggestions were that possible risk periods for intussusception could be 14–41 days after each dose of OPV (5, 6). Therefore, on the basis of previous work (6), we created four models, each defined to ensure that the risk periods did not overlap. The first model examined periods of 14–27 days and 28–41 days separately for each dose. The second model examined the two periods (14–27 days and 28–41 days) separately, using data from all doses combined. The third model examined a 14– to 41-day period after each OPV dose, and the last model examined a 14– to 41-day period using data from all doses combined. Because several studies showed a strong association between rotavirus vaccine and intussusception 3–7 days after vaccination (1–3), SCCS analysis was also used for the period 3–21 days after OPV, with risk periods of 3–7 days after vaccination and 8–21 days after vaccination. In addition, since there was a change in the recommended age of OPV vaccination in 1990 (when the 3-, 5-, and 10-month schedule was altered to an accelerated 2-, 3-, and 4-month schedule), analyses using both sets of the above models were carried out separately for cases in which the first vaccination dose was administered before or after January 1990.

The risk of obtaining inflated relative incidence estimates because of the “healthy vaccinee effect” (15), where children who have had intussusception are less likely to receive OPV shortly afterwards, has been highlighted by other studies (6). We examined this potential effect by defining the 2 weeks prior to vaccination as a separate risk period that was not included in the control periods, since incidence of intussusception is likely to be lower then. A similar approach has been adopted in case-crossover studies, which also use the self-control methodology to assess the risk of vaccine-associated adverse events but use paired risk and control period data to generate odds ratios (16). The results are not shown, because they did not significantly alter the findings.
RESULTS

In 1987–1999, there were 892 hospitalizations for intussusception involving 619 infants, producing an average annual rate of 110 episodes per 100,000 infants under age 1 year and 76.3 first episodes per 100,000 infants under age 1 year. The highest incidence was in children aged 3–6 months. These results are in the range found in a recent World Health Organization review (4). We selected only the patient’s first intussusception record for further analysis, to minimize the risk of overestimating the relative incidence of disease through the existence of multiple episodes per person within risk periods.

Probability matching resulted in 82.2 percent \((n = 509)\) of hospitalization records linking to vaccination records. The remaining 17.8 percent \((n = 110)\) of hospitalization records failed to match, mainly because of unavailability of vaccination data from the three nonparticipating areas. A further 43 records were omitted from subsequent analysis because of missing OPV dose data, leaving 466 cases in the final analysis. Figure 1 shows the breakdown of ages at intussusception for these cases, which comprised 290 (62 percent) males and 176 (38 percent) females. The cases showed no clear seasonality.

Risk period 14–41 days (1987–1999)

Table 1 shows that the only periods with statistically significant changes in relative incidence were in models 1 and 3, which investigated each dose individually. Model 1 showed a significantly reduced relative incidence of intussusception (relative incidence \((RI) = 0.51, 95\text{ percent CI: }0.29, 0.89\)) for days 14–27 after the first dose. Similarly, model 3 showed a significantly reduced relative incidence \((RI = 0.69, 95\text{ percent CI: }0.48, 1.00)\) for the longer 14- to 41-day period after the first dose.

Risk period 3–21 days (1987–1999)

Results from the second set of models, with risk periods 3–7 days after vaccination and 8–21 days after vaccination, are shown in table 2. Model 1 indicated a significantly increased relative incidence in the 3–7 days after the first dose \((RI = 1.82, 95\text{ percent CI: }1.05, 3.14)\). Models 1 and 3 indicated a reduced relative incidence in the 3–7 days after the third dose \((RI = 0.23, 95\text{ percent CI: }0.06, 0.89)\) and the 3–21 days after the third dose \((RI = 0.56, 95\text{ percent CI: }0.35, 0.90)\), respectively. Finally, a reduced relative incidence \((RI = 0.72, 95\text{ percent CI: }0.54, 0.96)\) was found for the 8–21 days after vaccination (all doses combined) in model 2.

Pre-1990 cases

Analysis of the small number of pre-1990 cases \((n = 81)\) showed no significant risk of intussusception in any of the risk periods following vaccination, irrespective of which model was used.

Post-1990 cases

Results for the 385 post-1990 cases were similar to those in tables 1 and 2. The significant findings included a reduced relative incidence within 14–27 days of the first dose \((RI = 0.51, 95\text{ percent CI: }0.27, 0.96)\), an increased relative incidence within 3–7 days of the first dose only \((RI = 1.96, 95\text{ percent CI: }1.04, 3.70)\), and a reduced relative incidence after the third dose at both 3–7 days and 3–21 days \((RI = 0.25 (95\text{ percent CI: }0.06, 0.96)\text{ and }RI = 0.59 (95\text{ percent CI: }0.36, 0.95))\), respectively.

DISCUSSION

This study, which used national hospitalization data linked to vaccination records, provided no overall evidence...
for an association between OPV and intussusception. Of the 24 risk periods examined, relative incidence was unchanged for 18, significantly decreased for five (14–27 or 14–41 days after the first dose, 3–7 or 3–21 days after the third dose, and 8–21 days after any dose), and significantly increased for only one (3–7 days after the first dose). None of the six analyses of all doses combined showed a significantly increased risk, and one showed a significantly decreased risk.

There are several possible explanations for the finding of a significantly increased relative incidence 3–7 days after the first dose. Firstly, it could be an artifact of multiple hypothesis testing. Secondly, cases of intussusception in susceptible infants which would have occurred later anyway, in the absence of vaccination, could have been triggered by OPV. Thirdly, it could be a real effect. Of these three possibilities, the third is the least likely. It is striking that this significant result occurs in the same risk period and after the same dose

TABLE 1. Relative incidence of intussusception 14–41 days after receipt of oral polio vaccine, Scotland, 1987–1999

<table>
<thead>
<tr>
<th>Model and dose</th>
<th>No. of days after oral polio vaccine</th>
<th>No. of events</th>
<th>RI*</th>
<th>95% CI*</th>
<th>No. of events</th>
<th>RI</th>
<th>95% CI</th>
<th>No. of events</th>
<th>RI</th>
<th>95% CI</th>
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<td></td>
<td>14–27</td>
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<tr>
<td>1</td>
<td>First</td>
<td>14</td>
<td>0.51</td>
<td>0.29, 0.89</td>
<td>26</td>
<td>0.85</td>
<td>0.55, 1.31</td>
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<td></td>
<td>Second</td>
<td>29</td>
<td>0.97</td>
<td>0.65, 1.44</td>
<td>35</td>
<td>1.23</td>
<td>0.85, 1.78</td>
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<td>Third</td>
<td>19</td>
<td>0.85</td>
<td>0.53, 1.37</td>
<td>21</td>
<td>0.94</td>
<td>0.60, 1.49</td>
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<td>2</td>
<td>All combined</td>
<td>62</td>
<td>0.78</td>
<td>0.59, 1.04</td>
<td>82</td>
<td>1.00</td>
<td>0.77, 1.31</td>
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<td>3</td>
<td>First</td>
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* RI, relative incidence; CI, confidence interval.


<table>
<thead>
<tr>
<th>Model and dose</th>
<th>No. of days after oral polio vaccine</th>
<th>No. of events</th>
<th>RI*</th>
<th>95% CI*</th>
<th>No. of events</th>
<th>RI</th>
<th>95% CI</th>
<th>No. of events</th>
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<th>95% CI</th>
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<tr>
<td>1</td>
<td>First</td>
<td>15</td>
<td>1.82</td>
<td>1.05, 3.14</td>
<td>16</td>
<td>0.64</td>
<td>0.38, 1.09</td>
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<td>Second</td>
<td>10</td>
<td>0.93</td>
<td>0.49, 1.75</td>
<td>26</td>
<td>0.84</td>
<td>0.56, 1.27</td>
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<tr>
<td></td>
<td>Third</td>
<td>2</td>
<td>0.23</td>
<td>0.06, 0.89</td>
<td>16</td>
<td>0.67</td>
<td>0.40, 1.12</td>
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<tr>
<td>2</td>
<td>All combined</td>
<td>27</td>
<td>0.96</td>
<td>0.65, 1.43</td>
<td>58</td>
<td>0.72</td>
<td>0.54, 0.96</td>
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<tr>
<td>3</td>
<td>First</td>
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<td>4</td>
<td>All combined</td>
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* RI, relative incidence; CI, confidence interval.
as was found for rotavirus vaccine. However, no other epidemiologic study has found an association between OPV and intussusception 3–7 days after the first dose, and any statistically significant findings in other studies have been observed after different doses and in different time periods. Further, descriptive case series reports of intussusception have failed to provide any laboratory evidence of poliovirus. Therefore, the first explanation seems most likely.

To our knowledge, our study analyzed more linked cases \((n = 466)\) than any other study for which results have been reported. We also matched a higher percentage of intussusception cases to vaccination records \((82\%)\) than did other studies. The majority of intussusception cases that failed to be linked were for areas that did not participate in the vaccine recording system. One weakness of our study was that if three doses of OPV with complete information had not been recorded, the linked case was excluded from analysis. This means that if intussusception occurred after the first or second dose of OPV, possibly making it less likely for the infant to receive a third dose, the apparent risk of intussusception following the first or second dose would have tended to be underestimated. Another weakness was that, in common with some other epidemiologic studies, we were not able to review individual case notes to validate the International Classification of Diseases coding against case definitions, which have since been established \((17)\). However, the hospitalization data set we used is subject to more general quality assurance, which does include detailed case review. Case note review of hospitalizations coded for intussusception in the United Kingdom has previously confirmed the diagnosis in nearly 90 percent of cases \((6)\).

The period of 14–41 days after OPV vaccination was used as the risk period for initial hypothesis-generating and confirmatory studies \((5, 6)\). These studies were reviewed at a workshop in 2000, and the hypothesis of a causal relation was overwhelmingly rejected \((5)\). Apart from the derived output of initial data sets, it is unclear why a risk period of 14–41 days after vaccination was proposed, since it is known that poliovirus is established in the intestinal tract within 24–48 hours of administration, making an earlier risk period feasible \((18)\). However, SCCS studies in England and Cuba failed to find any significantly increased risk of intussusception 0–13 days \((RI = 0.98, 95\% CI: 0.41, 2.32; 218 linked cases)\) or 0–14 days \((RI = 0.94, 95\% CI: 0.47, 1.88; 273 linked cases)\) after vaccination \((6, 7)\). A further nested case-control study in England failed to find an increased risk of intussusception in the 1–7 days from the last OPV vaccination \((odds ratio = 0.9, 95\% CI: 0.4, 2.0; 133 cases)\) but did not examine each dose independently \((8)\). A lack of association was also found in more recent case-control studies from the United States \((9)\) \((odds ratio = 1.1, 95\% CI: 0.5, 2.2; 119 cases)\) and India \((19)\) \((odds ratio = 0.9, 95\% CI: 0.5, 1.3; 137 cases)\).

Statistically significant signals for increased risk of intussusception after administration of OPV have been raised in previously published studies \((5, 6)\), although these signals appeared after different doses and different time periods than in our study. The first was a cohort study in the United States using the Vaccine Safety Datalink network \((5)\). It found an increased risk 22–28 days after the second OPV dose, scheduled for age 4 months \((odds ratio = 2.6, 95\% CI: 1.3, 4.6; 137 cases)\). The second was the first SCCS study conducted in England, which found an increased risk 14–27 days after the third OPV dose, again scheduled for age 4 months \((RI = 1.97, 95\% CI: 1.2, 3.22; 218 linked cases)\) \((6)\). In the context of other studies that did not replicate these findings, particularly subsequent SCCS results for England, consensus opinion was for rejection of a causal association \((5)\). Nevertheless, the question remained intriguing as to why two large, independent linked databases from two countries with different OPV schedules both found significant increases in intussusception for doses of OPV scheduled at age 4 months, albeit in different risk periods. Our study found no increased risk after the third dose, scheduled for age 4 months, and indeed found a significant decrease in the periods 3–7 days and 3–21 days. This tends to confirm that the significant findings in both our study and the above two previous studies were probably due to chance or were artifacts of multiple hypothesis testing.

The absence of an association between OPV and intussusception is in marked contrast to findings for rotavirus vaccine, for which case series analysis showed a rate ratio of 29.4 \((95\% CI: 16.1, 53.6)\) and estimated one attributable case of intussusception for every 9,474 infants vaccinated \((3)\). Our study results provide further assurance of the safety of OPV vaccine, both for countries \((such as the United States and the United Kingdom)\) that used OPV for many decades before switching to inactivated versions and for countries that are still highly dependent on OPV for eventual polio eradication. Our study also demonstrates the effectiveness of linking comprehensive vaccination and hospitalization data sets, such as those in Scotland, for the investigation of proposed vaccine-associated adverse events. There is great potential for future research into other proposed vaccine-associated adverse events, using the same method. However, this essential postmarketing safety surveillance relies on the continued availability of individual patient data, the use and confidentiality of which has been much debated of late \((20)\).

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**REFERENCES**