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Background: The new rotavirus vaccines RV5 and RV1 have been associated with small increase in intussusception risk in active vaccine surveillance studies. It is unclear what the impact might be on the overall trends of intussusception hospitalizations at a large population basis.

Methods: We conducted an ecological study of hospital discharges of infants with intussusception discharge diagnosis using the California Office of Statewide Health Planning and Development database (1985–2010). We measured incidence rates (IR) of intussusception hospitalizations per 100,000 births within 3 periods (1985–1997; 2000–2005; 2006–2010) related to past, pre-introduction and post-introduction of the new rotavirus vaccines. We estimated slopes of yearly IRs within each period, changes in slopes between periods and IR ratios (IRR) of the mean IRs between periods. We did subgroup analyses for 5 age-subgroups. We also analyzed intussusception hospitalizations of infants who also had a surgical repair and/or radiologic reduction procedure code (restricted cohort).

Results: We identified 6241 intussusception hospitalizations; 4696 also had pertinent procedure codes. There was an upward trend in yearly IRs during 2006–2010 (+2 excess cases per 100,000 births per year; P = 0.023); the change in slopes between 2006–2010 and 2000–2005 was +3.2 excess cases per 100,000 births per year (P = 0.052), and the IR in 2006–2010 was 10% higher than in 2000–2005 (IRR: 1.10; 95% confidence intervals: 1.01–1.19). The IRR in 2006–2010 versus 2000–2005 for the 6–14 weeks age-subgroup was 1.90 (95% confidence intervals: 1.33–2.74). In the restricted cohort, trends were similar, though not nominally significant.

Conclusions: We documented at a population-level a small increased risk in intussusception hospitalizations post-introduction of the new rotavirus vaccines.

Key Words: intussusception hospitalizations, rotavirus vaccine, children, California, 1985–2010

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Intussusception is the most common cause of intestinal obstruction in infants <12 months of age; its etiology is often unknown. The RotaShield rotavirus vaccine, initially licensed in the US in 1998, was associated with increased risk for intussusception¹ and was withdrawn from the market in 1999.⁴ Two new rotavirus vaccines were subsequently licensed in the US in 2006 (Rotarix; RV5; Merck) and 2008 (Rotarix; RV1; GSK). Although several early post-2006 studies did not show an association with intussusception,¹⁰–¹⁶ more recent studies did show that these new rotavirus vaccines are also associated with a small increased intussusception risk,¹⁰–¹⁶ although much lower than with RotaShield. Attributable risk estimates were consistent, ranging between 1 and 5 excess intussusception cases per 100,000 vaccinated infants¹⁵,¹⁶; however, there is still some uncertainty in the point estimates. Moreover, it is unknown how big an impact such risks could have on the overall rate of hospitalizations because of intussusception at a population level.

Availability of hospital discharge data on the large and diverse population of California makes it possible to check for patterns in intussusception epidemiology at a population level, precarious and postlicensure of the new rotavirus vaccines.

METHODS

Study Design and Identification of Cases

We performed an ecological study using the Office of Statewide Health Planning and Development (OSSHD) database¹⁷ that has data for inpatient discharges from all State licensed hospitals in California from 1985 to 2010. We searched the database for discharges from acute care facilities of infants admitted at age <1 year with a discharge diagnosis code for intussusception according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM code 560.0). We extracted information for admission year, age at admission (days), gender, race/ethnicity, principal discharge diagnosis code and up to 24 additional diagnosis codes and principal procedure code and up to 20 additional procedure codes.

Analyses

In our primary analysis, we used the whole cohort of hospitalized infants with an ICD9 diagnosis code for intussusception (primary cohort). Identification of intussusception cases by this ICD9 diagnosis code has been used by several earlier cohort studies.⁸,⁹,¹⁵,¹⁶ We kept the same definition to maintain comparability in the results. We analyzed also a subgroup of infants who not only had a discharge diagnosis code for intussusception but also had a surgical repair and/or radiologic reduction procedure code pertinent for intussusception (restricted cohort). By using these more strict inclusion criteria we tried to exclude rule-out intussusception cases. Procedure codes were used in prior studies as a surrogate for the severity of intussusception,⁴ and only in the study by Yih et al.,¹⁶ a procedure code, for therapeutic enema, was also used for the intussusception case definition. Similar statistical analyses were performed for both the primary and the restricted cohorts.

We calculated the mean incidence rates (IRs) in 3 predefined study periods: period 1 (1985–1997), a period with only 1 live enteric virus vaccine (oral poliovirus vaccine) recommended in the U.S. childhood immunization schedule; period 2 (2000–2005), a period with no recommendation for any live enteric virus vaccine
and period 3 (2006–2010), a period post-introduction in the US of the 2 new rotavirus vaccines (RotaTeq in 2006 and Rotarix in 2008). The transition years 1998–1999, during which the first rotavirus vaccine RotaShield was in the national childhood immunization schedule in the US, until its withdrawal from the market in October 1999, were not included in the 3 analyzed periods. The total number of live births per year was extracted from the OSHPD database of hospital births.

Subsequently, we calculated (a) the slopes (and 95% confidence intervals thereof) of the yearly IRs of intussusception hospitalizations within each of the 3 predefined periods; (b) the changes in the slopes of the yearly IRs (and 95% confidence intervals thereof) between different periods (slope in 2006–2010 vs. slope in 2000–2005); (c) the IR ratio (IRR and 95% confidence interval thereof) of the mean IRs of intussusception hospitalizations between different periods.

We calculated the intussusception IRs per week of age separately for the 3 predefined periods. We calculated the intussusception IRs for 5 age subgroups (1–5; 6–14; 15–24; 25–32 and 33–52 weeks) across the 3 periods and the respective IRRs of the mean IRs/age subgroup between different periods. There is no consensus in the literature on the exact age subgroups to be studied for the identification of age dependent intussusception risk differences. We selected the same age subgroups as in previous literature.14 In an exploratory analysis, we also considered infants in the 34–40 weeks age subgroup, as the new rotavirus vaccines are not recommended to be given beyond 8 months of age and any vaccine-related intussusception is unlikely to occur beyond 4 weeks postvaccination.

Statistical Analyses

The slopes (trends) of the intussusception yearly IRs were calculated by using the Patrick Royston trend STATA module for analysis for trend [a nonparametric χ² statistic test for the trend (regression) of the proportion of intussusception hospitalizations: total live births over time]. The change in slopes between periods was calculated by using interrupted time series analyses with Auto-Regressive Integrated Moving Average (ARIMA) model (p, d, q) = (1, 0, 0). The IRs of the mean IRs between different periods were calculated by using the STATA immediate command irr. A type 1 error rate of 0.05 was used to determine statistical significance. All statistical analyses were done in STATA/SE 12 (StataCorp LP, College Station, TX).

RESULTS

Over the past 26 years in the OSHPD database, there were 13,849,663 live born infants in California hospitals (Figs., Supplemental Digital Content 1, http://links.lww.com/INF/C76). We identified a total of 6241 intussusception hospitalizations; 4696 (75%) also had a surgical repair and/or radiologic reduction procedure code; and 4491 cases had intussusception as their principal discharge diagnosis code (all those cases also had a surgical repair and/or radiologic reduction procedure code; Table 1). The highest IR was observed in children of Hispanic race, and this was consistently seen across the 26-year study period and across the 3 individual periods (Table 1 and Table, Supplemental Digital Content 2, http://links.lww.com/INF/C77).

Yearly Incidence Rate of Intussusception Hospitalizations

The yearly IRs of intussusception hospitalizations in the 3 predefined periods are shown in Figure 1. The mean IRs across the 3 study periods were 51 per 100,000, 37 per 100,000 and 41 per 100,000 live births. The mean IR in period 3 was 10% higher compared with period 2 (IRR 1.10; P = 0.028; although compared with period 1, the mean IRs in period 3 and in period 2 were both lower (Table 2). There was a statistically significant upward trend in the yearly IRs (by the Royston test for trend) in period 3 (slope: +2.0 excess cases per 100,000 birth per year; P = 0.023), whereas there was a statistically significant downward trend in period 1, and there was no statistically significant trend in period 2 (Table 2 and Fig. 1). There was a borderline statistically significant upward trend in the change in slopes (by the ARIMA model) of the yearly IR of intussusception hospitalizations between 2006–2010 and 2000–2005 (+3.2 cases per 100,000 births per year; P = 0.052; Table 2).

### TABLE 1. Infants Hospitalized with Intussusception in California (1985–2010)

<table>
<thead>
<tr>
<th>Cohort Characteristics</th>
<th>Intussusceptions</th>
<th>Incidence Rate† (per 100,000 births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary cohort*:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall period: 1985–2010</td>
<td>6241</td>
<td>45</td>
</tr>
<tr>
<td>Period 1: 1985–1997</td>
<td>3519</td>
<td>51</td>
</tr>
<tr>
<td>Period 2: 2000–2005</td>
<td>1187</td>
<td>37</td>
</tr>
<tr>
<td>Period 3: 2006–2010</td>
<td>1094</td>
<td>41</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3923</td>
<td>55</td>
</tr>
<tr>
<td>Females</td>
<td>2318</td>
<td>34</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2089</td>
<td>39</td>
</tr>
<tr>
<td>Black</td>
<td>418</td>
<td>47</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3136</td>
<td>54</td>
</tr>
<tr>
<td>Asian</td>
<td>329</td>
<td>26</td>
</tr>
<tr>
<td>Restricted cohort†:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical repair and/or radiologic reduction codes</td>
<td>4696/6241 (75%)</td>
<td>34</td>
</tr>
<tr>
<td>Only surgical repair codes</td>
<td>2502/6241 (40%)</td>
<td>18</td>
</tr>
<tr>
<td>Only radiologic reduction codes</td>
<td>1440/6241 (23%)</td>
<td>10</td>
</tr>
<tr>
<td>Both surgical repair and radiologic reduction codes</td>
<td>754/6241 (12%)</td>
<td>5</td>
</tr>
<tr>
<td>No pertinent procedure-codes</td>
<td>1545/6241 (25%)</td>
<td>11</td>
</tr>
<tr>
<td>Restricted cohort‡:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 1: 1985–1997</td>
<td>2854/3519 (81% ‖)</td>
<td>41</td>
</tr>
<tr>
<td>Period 2: 2000–2005</td>
<td>820/1187 (69% ‖)</td>
<td>26</td>
</tr>
<tr>
<td>Period 3: 2006–2010</td>
<td>700/1094 (64% ‖)</td>
<td>26</td>
</tr>
<tr>
<td>Hospitalized infants with a principal discharge diagnosis code for intussusception</td>
<td>4491/6241 (72%)</td>
<td>32</td>
</tr>
</tbody>
</table>

Intussusceptions during 1988–1999, when the rotavirus vaccine RotaShield was administered, were not included in the data for the 3 individual periods (441 cases for the primary cohort and 322 cases for the restricted cohort).

*Primary cohort: includes infants with intussusception hospital discharge diagnosis code (ICD9 560.0).†Restricted cohort: includes infants with intussusception hospital discharge diagnosis code (ICD9 560.0) and associated surgical repair and/or radiologic reduction procedure codes. The identification of surgical repair and radiologic reduction procedure codes for the restricted cohort analysis was done by screening all procedure codes assigned to more than 20 patients with ICD9-codes for intussusception; 7 pertinent surgical repair and 4 radiologic reduction procedure codes were finally considered.

Surgical repair procedure codes: Codes 46.80–42 for intra-abdominal manipulation of intestine not otherwise specified; for intra-abdominal manipulation of small intestine and for intra-abdominal manipulation of large intestine respectively; code 45.72 for open cecectomy; code 54.11 for exploratory laparotomy. Radiologic reduction procedure codes: Code 96.29 for reduction of intussusception of alimentary tract; code 87.64 for lower gastrointestinal series; code 96.39 for other transanal enema and 46.85 for dilation of intestine.

†Incidence rates per gender and race were calculated per 100,000 live births of same gender and race respectively.

‡All 4491 cases with intussusception as their principal discharge diagnosis code also had a surgical repair and/or radiologic reduction procedure code. The percentages correspond to the ratio of the individuals in the restricted cohort compared with the individuals in the primary cohort, across those periods.
Subgroup Analyses

The mean intussusception IRs in the restricted cohort of the 4696 intussusception cases with surgical repair and/or radiologic reduction procedure codes in the 3 periods were 41 per 100,000, 26 per 100,000, and 26 per 100,000 live births. Across the 26-year study period, intussusception cases with only a surgical repair procedure code decreased by 36% (from IR 22 to 14 per 100,000 live births; \( P < 0.001 \)), whereas intussusception cases with only a radiologic reduction procedure code decreased by 8% (from IR 12 to 11 per 100,000 live births; \( P = 0.027 \); Fig., Supplemental Digital Content 3, http://links.lww.com/inF/C78). The decline, however, was limited to the years 1985–2005 and was followed by a steady increase in the following years.

The slope of the yearly IR of intussusception hospitalizations with surgical repair and/or radiologic reduction procedure codes (by the Royston test for trend) showed a nonstatistically significant
upward trend in period 3 (slope: +1.3 excess cases/100,000 births per year; \(P = 0.062\)), whereas there was a statistically significant downward trend in the 2 preceding periods. The change in slopes of the yearly IRs of intussusception hospitalizations with surgical repair and/or radiologic reduction procedure codes between 2006–2010 and 2000–2005 (by the ARIMA model) showed a nonstatistically significant increase by +3.2 excess cases per 100,000 births per year (\(P = 0.178\); Table 2). There was no statistically significant difference in period 3 versus period 2 in the mean IRs of intussusception hospitalizations with surgical repair and/or radiologic reduction procedure codes (IRR 1.02; \(P = 0.76\); Table 2).

**Intussusception Incidence Rates Per Week of Age**

Across the 26-year study period, the highest IR per week of age (per 100,000 births) occurred at 25 weeks. The IR per week of age according to period is shown in Figure 2 and Figure, Supplemental Digital Content 4, http://links.lww.com/INF/C79. In the age subgroup analyses, the highest IR was observed in the 25–32 weeks age subgroup (both for the primary and restricted cohorts). This was consistently seen across the whole 26-year study period and in the individual 3 periods (Tables, Supplemental Digital Content 5 and 6, http://links.lww.com/INF/C80 and http://links.lww.com/INF/C81).

In the age subgroup analysis in the primary cohort, a statistically significant difference between period 3 and period 2 was seen for the 6–14 weeks age subgroup, with mean IR in period 3 almost 2-fold higher compared with the IR in period 2 [IRR: 1.90; 95% confidence intervals (CIs): 1.33–2.74; \(P < 0.001\); Table, Supplemental Digital Content 6, http://links.lww.com/INF/C81]. A statistically significant difference between the last 2 periods was also detected for the 33–52 weeks age subgroup; however, when the narrower 33–40 weeks age subgroup was considered, no difference was seen.

In the restricted cohort, there were no statistically significant differences for any subgroup analysis between the last 2 periods.

**DISCUSSION**

In 2006–2010, post-introduction of the new rotavirus vaccines in the US, we detected a small, but demonstrable increase in the intussusception risk compared with the preceding period 2000–2005. This finding was consistent across different statistical analyses. In 2006–2010, there was a statistically significant upward trend in the yearly IRs of intussusception hospitalizations; despite a preceding downward nonsignificant trend in 2000–2005. There was a borderline statistically significant upward change in slopes in 2006–2010 versus 2000–2005 with +3.2 excess intussusception cases per 100,000 births per year. There was also a 10% statistically significant increase in the mean IR of intussusception hospitalizations in 2006–2010 versus 2000–2005.

The increased population level risk we detected is consistent with the small increased intussusception risk of approximately 1–5 excess intussusception cases per 100,000 vaccinated infants recently seen in 2 active vaccine surveillance projects in the US.\(^{15,16}\) Weintraub et al\(^{15}\) detected 5.3 excess intussusception cases per 100,000 vaccinated infants, after the first dose of the monovalent rotavirus vaccine, within the 1–7 days window period, whereas Yih et al\(^{16}\) detected 1.5 excess intussusception cases per 100,000 vaccinated infants, after the first dose of the pentavalent vaccine, within the 1–21 days window period. Similarly, small increase in intussusception risk postvaccination was also seen in a recent passive vaccine surveillance study in the US\(^{14}\) and additional vaccine surveillance studies in Mexico, Brazil\(^{10,11}\) and Australia.\(^{12,13}\) Our project offers a complementary population level confirmation of this recently seen small increased intussusception risk post-introduction of the new **FIGURE 2.** Incidence rates per week of age (per 100,000 live births) of intussusception hospitalizations across the 26-year study period and across the 3 individual periods (period 1: 1985–1997; period 2: 2000–2005; period 3: 2006–2010). (Shown are Kernel-weighted local polynomial smoothing-lines. Vertical dash-dot line corresponds to the week of age with the highest IR for the whole cohort across the 26 years.)
rotavirus vaccines. Such an increased risk was not reported in previous cohort studies with data up to 2009. The Yen et al study with data from the State Inpatient Databases from 26 states (including California) up to year 2009 showed a small increase in intussusception hospitalizations in 2007 compared with 2000–2005; whereas in 2008, there were no differences and in 2009, the intussusception hospitalizations were even slightly lower. The results in our study were consistent between the analyses in the primary cohort and the restricted cohort of infants in whom more strict criteria for intussusception diagnosis were applied, although in the restricted cohort they were less pronounced and did not reach statistical significance. In the restricted cohort, there was an upward trend in the yearly IR of intussusception hospitalizations in 2006–2010, despite a statistically significant decreasing trend in the IRs in the preceding 6 years. Moreover, in the restricted cohort, the size of the trend in 2006–2010 and the size of the change in trends between the last 2 periods were similar to those seen in the primary cohort, despite not reaching formal statistical significance. Furthermore, although in the restricted cohort, the mean IRs of intussusception hospitalizations in the last 2 periods were not statistically significant different, mean IRs do not capture within-period slopes and between-periods changes in slopes and give information only for the average estimates during each period. It is likely that the restricted cohort might have been underpowered to show statistically significant differences as only two-thirds of the infants were included.

However, an alternative explanation that could be considered is that the 25% of infants who did not have any intussusception related procedure code could have been rule-out intussusception cases, rather than true intussusception cases. This could reflect increased awareness among physicians post-2006 for potential intussusception risks associated with the new rotavirus vaccines. However, we could not test this hypothesis because we did not have access to the infants’ clinical notes in the medical records. The ICD-9-560.0 discharge diagnosis code for intussusception from Hospitals and Emergency Departments has an estimated positive predictive value of ~75%6,18; which could be considered consistent with our finding that only 75% of infants in the primary cohort also had an intussusception related procedure code. Nevertheless, true intussusception cases in the primary cohort without procedure codes could still have had procedures performed in outpatient settings before their hospitalization that would not have been captured in our database. In addition, possible differences in coding practices over time cannot be excluded.

Our study was an ecological study, and explanations of our findings based on immunization differences between period 3 and period 2 were based solely on ecological assumptions. Although we do not know the vaccination coverage rate specifically for the infants in our cohort, nationwide rotavirus vaccination coverage reached 71% in 2012 compared with 44% in 2009 for children 19–35 months of age, and nationwide, rotavirus vaccination coverage rate for infants <12 months of age was 73% during 2008–2009. We do not know whether the increased risk we observed would have been even stronger if, in the early years post-introduction of the new rotavirus vaccine, the vaccine coverage rates were higher. In an exploratory analysis, excluding the data from 2006–2010. an increased intussusception risk for the 6–14 weeks age subgroup was also seen in the population-level analyses by Yen et al, but only for the years 2007 and 2008, compared with 2000–2005; whereas for 2009, the signal remained significant only for the smaller age subgroup 8–11 weeks. In addition, the 6–14 weeks age subgroup includes the period during which a signal for increased intussusception risk was also recently documented in the U.S. active vaccine surveillance studies by Weintraub et al and Yih et al in additional studies in Australia and Mexico. Increased intussusception risk in the same age subgroup was also observed after the first dose of the old rotavirus vaccine (RotaShield). In periods 2 and 3, the highest IRs per week of age occurred in infants older than 25 weeks, whereas in period 1, the highest IRs occurred in infants younger than 25 weeks. However, this is possibly a chance finding due to multiple comparisons and does not represent a vaccine-associated effect as it was observed both in 2000–2005 and in 2006–2010.

In summary, after the introduction of the new rotavirus vaccines, we identified an upward trend in yearly IRs of intussusception hospitalizations in 2006–2010. There was also a borderline statistically significant incremental change in the yearly IRs in 2006–2010 compared with the preceding period 2000–2005 and a 10% relative increase in the mean IR in 2006–2010 versus 2000–2005. The age subgroup with the highest intussusception IR ratio in 2006–2010 versus 2000–2005 was the 6–14 weeks age subgroup. The population level signal we detected provides complementary supporting information to the information generated by active vaccine safety surveillance projects.


