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(See the editorial commentary by Clarke and Marshall, on pages 3–5.)

Background. Although US data have not documented an intussusception risk with current rotavirus vaccines, international data indicate a possible low risk, primarily after the first dose.


Results. Compared with 2000–2005 (35.3 per 100 000), the rate was greater in 2007 (39.0 per 100 000; rate ratio [RR], 1.10; 95% confidence interval [CI], 1.04–1.18), similar in 2008 (33.4 per 100 000; RR, 0.95; 95% CI, .89–1.01), and lower in 2009 (32.9 per 100 000; RR, 0.93; 95% CI, .87–.99). Among infants aged 8–11 weeks, compared with 2000–2005 (6.9 per 100 000), a small, significant increase was observed in each of 2007 (11.4 per 100 000; RR, 1.64; 95% CI, 1.08–2.50), 2008 (12.2 per 100 000; RR, 1.76; 95% CI, 1.17–2.65), and 2009 (11.0 per 100 000; RR, 1.59; 95% CI, 1.04–2.44).

Conclusions. Following rotavirus vaccine introduction, a small increase in intussusception rates was seen among US infants aged 8–11 weeks, to whom most first doses of vaccine are given; no sustained population-level change in overall rates was observed.

In 1999, a rhesus-human reassortant tetravalent rotavirus vaccine (RotaShield; Wyeth Lederle Vaccines) was withdrawn from the US market <1 year after its licensure due to an association with intussusception at a rate of 1 case per 10 000 vaccinated infants, particularly after the first dose of vaccine [1–4]. Because of this association, the 2 rotavirus vaccines currently licensed in the United States—a bovine-human reassortant rotavirus vaccine (RotaTeq [RV5]; Merck and Company) licensed in 2006 and an attenuated human monovalent rotavirus vaccine (Rotarix [RV1]; GlaxoSmithKline Biological) licensed in 2008—underwent large prelicensure trials of approximately 60 000–70 000 infants each. RV5 is given orally in 3 doses before the age of 8 months, and RV1 is given orally in 2 doses before the age of 8 months. In the United States, the Advisory Committee on Immunization Practices recommends that for both vaccines the first dose of vaccine be given no earlier than age 6 weeks and no later than age 14 weeks and 6 days. No increased risk for intussusception was observed with either vaccine in the time window examined (0–42 days after each of 3 RV5 doses and 0–31 days following each of 2 RV1 doses) [5–7].
However, recent data from postlicensure monitoring in Mexico and Australia indicate a risk of intussusception with the current rotavirus vaccines of lower magnitude (approximately 1 to 2 cases per 100,000 vaccinated infants) than RotaShield, primarily within the first week after the first vaccine dose [8–11]. A risk of this magnitude has not been documented in the United States [12–14]; however, available US data are insufficient to confidently exclude the low-level risk seen in Mexico and Australia.

Whether or not wild-type rotavirus is responsible for some cases of intussusception in infancy is not clear [15, 16]. However, such an association seems biologically plausible because both current rotavirus vaccines [5–7] and the previous RotaShield vaccine [1–4] that are each based on different rotavirus strains have been linked to intussusception. Additionally, some findings have suggested that rotavirus vaccination may decrease the incidence of intussusception later in infancy, perhaps by protection from intussusception caused by wild-type rotavirus infection. For example, data from a 1-year follow-up of a subset of infants enrolled in the RV1 clinical trial in Latin America showed a significantly reduced risk (relative risk, 0.28; 95% confidence interval [CI], 0.10–0.81) of intussusception among vaccine recipients compared with placebo recipients [17]. In addition, ecologic assessments during the period when RotaShield vaccine was used were unable to detect an overall population-level increase in intussusception hospitalizations in US infants, despite a much higher estimated risk of intussusception with RotaShield compared with current rotavirus vaccines [18–20].

To fully assess the impact of rotavirus vaccination on intussusception in US infants, it is therefore important to examine both the possibility of an increased incidence of intussusception shortly after vaccination as well as a reduced incidence later in infancy. Since RV5 was introduced in the United States in 2006 and RV1 was subsequently introduced in 2008, rotavirus vaccine coverage among infants aged <12 months has increased slowly, with the majority of infants receiving vaccine doses within the recommended age windows [21, 22]. According to vaccination coverage data from 8 sentinel immunization sites located within the United States, first-dose rotavirus vaccine coverage rose from 50%–60% in the first year following introduction to approximately 72% in 2009 [21]. We conducted an ecological study to examine population-level trends in intussusception before and after introduction of rotavirus vaccine among infants from 26 states accounting for 75% of the US birth cohort for the period 2000–2009. We assessed overall trends in intussusception incidence among infants aged <12 months and also specifically among infants in the recommended age groups for receipt of rotavirus vaccination (6–14 weeks for the first dose, 15–24 weeks for the second dose, and 25–34 weeks for the third dose) [8–10].

MATERIALS AND METHODS

We defined an intussusception hospitalization as one with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for intussusception (560.0) listed as a discharge diagnosis. Additionally, we defined an intussusception hospitalization requiring surgical intervention as one with an ICD-9-CM procedure code of 450–489 or 540–542 listed as a procedure performed during the hospitalization.

Data Sources

Hospitalization Data

We analyzed data from the State Inpatient Databases (SID) maintained by the Healthcare Cost and Utilization Project (HCUP) to perform a retrospective, ecologic study of intussusception hospitalizations among infants aged <12 months from 2000 through 2009. Sponsored by the Agency for Healthcare Research and Quality, the HCUP is a collection of healthcare databases that provides multistate, discharge-level healthcare data through a federal-state-industry partnership [23]. The complete SID contain inpatient discharge data from 44 participating states in the United States. Because the number of states providing data changed during the study period, we restricted our analyses to 26 states that provided consistent data each year from 2000 through 2009. Of these 26 states, 4 were located in the Northeast (Connecticut, Massachusetts, New Jersey, and New York), 6 were located in the Midwest (Illinois, Iowa, Kansas, Michigan, Missouri, and Wisconsin), 9 were located in the South (Florida, Georgia, Kentucky, Maryland, North Carolina, South Carolina, Tennessee, Texas, and West Virginia), and 7 were located in the West (Arizona, California, Colorado, Hawaii, Oregon, Utah, and Washington). These states represent approximately 75% of the US birth cohort.

Population Data

We calculated intussusception hospitalization rates using the National Center for Health Statistics’ bridged-race postcensal population estimates for 2000 through 2009 for the 26 states included in the analysis [24]. We assumed births to be evenly distributed throughout the year when calculating hospitalization rates by age in weeks.

Analysis

We examined trends over time in the total number and rate of intussusception hospitalizations from 2000 through 2009. We then examined trends in intussusception hospitalization rates by nonoverlapping age groups based on the recommended ages for rotavirus vaccine doses (6–14 weeks for the first dose, 15–24 weeks for the second dose, and 25–34 weeks for the third dose). We further examined intussusception hospitalization rates among infants aged 8–11 weeks, to whom
approximately 83% of first doses of rotavirus vaccine are administered (P. Smith, CDC, personal communication).

We compared intussusception hospitalization rates during prerotavirus vaccine introduction years 2000–2005 with those during postrotavirus vaccine introduction years 2007–2009 by age. For these comparisons, we excluded data from 2006 because rotavirus vaccine was introduced into the national immunization schedule partway through the year. We computed rate ratios (RRs) and 95% CIs using SAS statistical software, version 9.2. P values <.05, calculated using Poisson regression analysis, were deemed statistically significant.

RESULTS

Intussusception Epidemiology and Trends Among Infants Aged <12 Months, 2000–2009

From 2000 through 2009, the 26 states included in the analysis reported a total of 10,836 intussusception hospitalizations among infants aged <12 months. From 2000 through 2006, rates remained relatively stable, ranging 33.1–36.5 intussusception hospitalizations per 100,000 infants (Figure 1). In 2007, the intussusception hospitalization rate increased to 39.0 per 100,000 infants but returned to baseline rates of 33.4 and 32.9 per 100,000 in 2008 and 2009, respectively. No seasonal variation or visual clustering of intussusception hospitalizations was noted. Rates of surgically treated intussusception also remained relatively stable from 2000 through 2006, with a range of 16.8–19.6 cases per 100,000 infants. This rate remained similar at 19.3 per 100,000 in 2007 and then decreased to 15.7 and 15.8 per 100,000 infants in 2008 and 2009, respectively. The fatality rate among infants hospitalized for intussusception remained close to zero (range, 0.0% in 2000 and 2006 to 0.2% in 2003 and 2007) for the entire study period (data not shown).

Age-Specific Trends in Intussusception Hospitalizations

Examination of rates of intussusception hospitalizations from 2000 through 2009 stratified by age group showed no uniform trends over time (Figure 2). Among infants aged 6–14 weeks, the average prevaccine intussusception hospitalization rate from 2000 through 2005 was 10.2 hospitalizations per 100,000 infants (range, 7.8–11.7 hospitalizations per 100,000) (Figure 3A). In postvaccine years 2007 and 2008, rates of intussusception hospitalizations among infants aged 6–14 weeks were greater than the average rate for the prevaccine years (13.4 hospitalizations per 100,000 infants in 2007 and 15.8 per 100,000 in 2008). However, in 2009, the intussusception hospitalization rate returned to a level similar to that during prevaccine years (12.0 hospitalizations per 100,000). Among the subset of infants aged 8–11 weeks, the average prevaccine-introduction intussusception hospitalization rate from 2000 through 2005 was 6.9 hospitalizations per 100,000 infants (range, 4.7–9.1 hospitalizations per 100,000) (Figure 3B). For these infants, intussusception hospitalization rates during all 3 postvaccine introduction years were greater than the

Figure 1. Trends in intussusception hospitalization among infants aged <12 months during 2000–2009, based on data from the State Inpatient Databases. Data are from 26 states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, North Carolina, New Jersey, New York, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, West Virginia, and Wisconsin.
prevaccine introduction average rate (11.4 hospitalizations per 100,000 infants in 2007, 12.2 per 100,000 in 2008, and 11.0 per 100,000 in 2009).

Rate ratios comparing intussusception hospitalization rates before and after rotavirus vaccine introduction, stratified by recommended ages for rotavirus vaccine doses, demonstrated that infants aged 6–14 weeks had significantly higher rates of hospitalization in postvaccine introduction years 2007 (RR, 1.32; 95% CI, 1.02–1.69; \( P = .03 \)) and 2008 (RR, 1.55; 95% CI, 1.22–1.97; \( P < .001 \)) but not in 2009 (RR, 1.18, 95% CI, 0.91–1.54; \( P = .22 \)), when compared with the average prevaccine rate from 2000 through 2005 (Table 1). Among the subset of infants aged 8–11 weeks, however, rates of hospitalization were higher in all postvaccine introduction years—2007 (RR, 1.64; 95% CI, 1.08–2.50; \( P = .02 \)), 2008 (RR, 1.76; 95% CI, 1.17–2.65; \( P < .001 \)), and 2009 (RR, 1.59; 95% CI, 1.04–2.44; \( P = .03 \))—when compared with the average prevaccine rate from 2000 through 2005.

For infants aged 15–24 weeks and 25–32 weeks, intussusception hospitalization rates tended to be lower in postvaccine years but were not significantly different compared with average prevaccine rates. The overall intussusception hospitalization rate for infants aged <12 months was slightly higher in 2007 (RR, 1.10; 95% CI, 1.04–1.18; \( P = .001 \)), when compared with the average prevaccine rate from 2000 through 2005 (Table 1), whereas rates in 2008 (RR, 0.95; 95% CI, 0.89–1.01; \( P = .09 \)) and 2009 (RR, 0.93; 95% CI, 0.87–0.99; \( P = .03 \)) subsequently decreased.

**DISCUSSION**

An increase in intussusception hospitalization rates was seen among infants aged 8–11 weeks, to whom most first doses of rotavirus vaccine are given, in each of the 3 post-vaccine introduction years. However, this finding was based on a relatively small number (approximately 30 per year) of intussusception cases in this age group, which may also explain why a similar trend was not seen among infants aged 6–14 weeks (ie, increase in rates in 2007 and 2008, but not in 2009). Furthermore, intussusception rates in infants aged 8–11 weeks did not progressively increase during each year from 2007 through 2009, which would be expected if the vaccines were associated with intussusception, given the increasing vaccine coverage in infants each year, from 64% in 2007 to 73% in 2009 [25]. In addition, our data show no consistent, overall population-level change in intussusception hospitalization rates among US infants following implementation of the rotavirus vaccination program. Compared with prevaccine years, the overall intussusception hospitalization rate among all infants aged <12 months increased slightly in 2007, the year after rotavirus vaccine was implemented, but rates were similar to prevaccine levels in 2008 and lower in 2009, despite increasing rotavirus vaccine coverage in US infants over this period. Nevertheless, the finding of a low-level increased risk of intussusception in the age group receiving most first rotavirus vaccine doses warrants further monitoring because a causal association cannot be established or excluded by this ecologic analysis alone.
To date, additional postlicensure epidemiologic assessments of rotavirus vaccine in the United States have not documented an increased risk of intussusception [12]. In the Vaccine Safety Datalink (VSD), which allows linkage of intussusception outcome data with rotavirus vaccination status for children enrolled in 8 health maintenance organizations that cover approximately 3% of the US population, 1 case of intussusception occurring within the first week after RV5 administration was identified among >300,000 administered first doses of RV5 [12]. This rate was similar to that seen in a concurrently enrolled cohort of children who did not receive rotavirus vaccine and also was within the limits of background rates expected based on prevaccine data from the VSD, but confidence limits were wide. Data from the passive US Vaccine Adverse Event Reporting System (VAERS) are harder to interpret due to limitations such as incomplete reporting of intussusception cases and lack of accurate data on doses of rotavirus vaccine administered to US infants. Although VAERS data do not demonstrate an increased risk of intussusception, a temporal clustering of reported intussusception cases in the first week after the first dose of RV5 has been observed, and the possibility of a low-level risk cannot be excluded with the VAERS or VSD data [14]. Uptake of RV1 has not reached a level of coverage that would enable an increased risk of intussusception to be detected by either of these systems. Additionally, a study examining hospitalization data from a similar database as that used in our study but over a smaller number of pre- and post-vaccination years also did not see an overall increase in intussusception hospitalizations among infants aged <12 months in the United States [26]. However, the authors were unable to...
examine specific age groups and so were not able to comment on intussusception trends among infants in age groups related to rotavirus vaccine doses.

Clear explanations as to why assessments in the United States have not found an increased risk for intussusception following rotavirus vaccination that have been observed in some other settings have not been established. However, possible explanations include differences in the natural risk of intussusception, infant diet, breastfeeding practices, and maternal antibody levels, all of which have been purported to be potential risk factors for intussusception following rotavirus vaccination [10, 27, 28]. Another possibility is that rotavirus vaccination coverage in the United States is not yet high enough to detect a potential increased risk; Australia and Mexico have reported higher vaccination coverage rates [29, 30]. Thus, it is also important to note that, despite data on >300 000 infants given a first dose of RV5 in the VSD, a low-level risk of 1 case per 50 000–100 000 infants seen in Mexico following the first dose of RV1 cannot be reliably excluded. Even so, if such a low-level risk of intussusception should exist in the United States, approximately 50 excess intussusception hospitalizations would occur each year in US infants compared with approximately 55 000–70 000 rotavirus-related hospitalizations each year [5], translating to the occurrence of approximately 1 excess intussusception hospitalization per 1100 to 1400 rotavirus-related hospitalizations. This increase in intussusception hospitalizations would be substantially outweighed by the well-documented benefits of rotavirus vaccination in US children, such as the prevention of an estimated 40 000–60 000 gastroenteritis-related hospitalizations in 2008 among US children aged <5 years and prevention of diarrheal disease burden as documented by many other studies conducted in the United States following rotavirus vaccine introduction [25, 31–36]. Furthermore, we noted that rates of intussusception hospitalizations among older infants tended to be lower in postvaccine years compared with prevaccine years, although these differences were not statistically significant. Further monitoring is needed to confirm whether intussusception rates later in infancy are decreased in vaccinated infants and, if observed, whether this decline could offset, at the population-level, any potential short-term increase in intussusception after vaccination.

Table 1. Rates of Intussusception Hospitalization Among Infants Aged <12 Months in 2007–2009 as Compared With the 2000–2005 Prevaccine Mean Baseline, Based on Data from the State Inpatient Databases

<table>
<thead>
<tr>
<th>Intussusception Hospitalizations</th>
<th>2000–2005 Rate per 100 000 (annual average no.)</th>
<th>2007 Rate per 100 000 (no. of cases) Rate Ratio (95% CI)</th>
<th>2008 Rate per 100 000 (no. of cases) Rate Ratio (95% CI)</th>
<th>2009 Rate per 100 000 (no. of cases) Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6–14 weeks</td>
<td>10.2 (53)</td>
<td>13.4 (74) 1.32 (1.02–1.69)</td>
<td>15.8 (87) 1.55 (1.22–1.97)</td>
<td>12.0 (66) 1.18 (0.91–1.54)</td>
</tr>
<tr>
<td>8–11 weeks</td>
<td>6.9 (16)</td>
<td>11.4 (28) 1.64 (1.08–2.50)</td>
<td>12.2 (30) 1.76 (1.17–2.66)</td>
<td>11.0 (27) 1.59 (1.04–2.44)</td>
</tr>
<tr>
<td>15–24 weeks</td>
<td>39.9 (230)</td>
<td>42.1 (259) 1.05 (0.92–1.20)</td>
<td>37.7 (231) 0.94 (0.82–1.08)</td>
<td>34.7 (212) 0.87 (0.75–1.00)</td>
</tr>
<tr>
<td>25–34 weeks</td>
<td>69.4 (320)</td>
<td>68.0 (335) 0.98 (0.87–1.10)</td>
<td>57.7 (283) 0.83 (0.73–0.94)</td>
<td>64.4 (315) 0.92 (0.82–1.05)</td>
</tr>
<tr>
<td>All &lt;12 months</td>
<td>35.3 (1060)</td>
<td>39.0 (1253) 1.10 (1.04–1.18)</td>
<td>33.4 (1069) 0.95 (0.89–1.01)</td>
<td>32.9 (1048) 0.93 (0.87–0.99)</td>
</tr>
</tbody>
</table>

Data are from 26 states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, North Carolina, New Jersey, New York, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, West Virginia, and Wisconsin.

Abbreviation: CI, confidence interval.
restricted all analyses to states providing data throughout the study period, our findings may not be generalizable to all US infants. However, because 75% of the US birth cohort was represented by a geographically diverse distribution of participating HCUP states, it is likely that a representative sample of US infants was included in the analyses. Finally, although management of intussusception may occur in nonpatient settings, such as with short stay or emergency department care [37–39], our analyses included only hospitalization data because emergency department data were unavailable for all states during our study period. Possible increased management of intussusception in nonpatient settings could have affected trends over time, although examination of data from the subset of states with both inpatient and nonpatient data did not indicate any specific patterns.

CONCLUSIONS

A small increase in intussusception rates was seen among infants aged 8–11 weeks, to whom most first doses of rotavirus vaccine were given, but no sustained population-level change in overall intussusception hospitalizations rates in US infants was observed after implementation of the US rotavirus vaccination program. Although an association between intussusception and rotavirus vaccination cannot be established by this ecologic analysis alone, even if the low risk with the first dose exists, it is outweighed by the well-documented benefits of vaccination of US infants [31].

Notes

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