

Intussusception Rates Before and After the Introduction of Rotavirus Vaccine

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abstract

BACKGROUND: Recent US studies have identified a small increased risk of intussusception after rotavirus vaccination, mainly after the first dose. We examined trends in intussusception hospitalizations before (2000–2005) and after (2007–2013) rotavirus vaccine introduction to assess whether this observed temporal risk translates into more hospitalized cases at the population level.

METHODS: Intussusception hospitalizations in children <12 months of age were abstracted from the State Inpatient Database maintained by the Healthcare Cost and Utilization Project for 26 states that provided data from 2000 to 2013. Rates were calculated using bridged-race postcensal population estimates. Trends were analyzed by age groups (6–14 weeks, 15–24 weeks, and 25–34 weeks) based on the recommended ages for vaccine administration as well as 8–11 weeks when the majority of first doses are given. Rate ratios were calculated by using Poisson regression.

RESULTS: No consistent change in intussusception hospitalization rates was observed among all children <12 months of age and among children 15 to 24 weeks and 25 to 34 weeks of age. The intussusception hospitalization rate for children aged 8 to 11 weeks was significantly elevated by 46% to 101% (range: 16.7–22.9 per 100 000) in all postvaccine years except 2011 and 2013 compared with the prevaccine baseline (11.7 per 100 000).

CONCLUSIONS: The increase in the intussusception hospitalization rate in children 8 to 11 weeks when the majority of first doses of vaccine are given is consistent with recent US postlicensure studies. Given the magnitude of declines in rotavirus disease compared with this small increase in intussusception, the benefits of rotavirus vaccination outweigh the increase risk of intussusception.

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Dr Tate conceptualized and designed study, conducted the analyses, interpreted the data, and drafted the initial manuscript; Drs Yen, Steiner, Cortese, and Parashar conceptualized and designed study, interpreted the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Healthcare Research and Quality.

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WHAT'S KNOWN ON THIS SUBJECT: Recent postmarketing studies in the US have identified a small increased risk of intussusception associated with rotavirus vaccination, mainly in the first week after the first dose. An estimated 1 to 5 excess cases of intussusception occur per every 100 000 children vaccinated.

WHAT THIS STUDY ADDS: No consistent change in intussusception hospitalization rates was observed among all children <12 months of age but the rate for children 8 to 11 weeks was significantly elevated 46% to 101% in all postvaccine years except 2011 and 2013 compared with prevaccine baseline.

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In 1999, a rotavirus vaccine (RotaShield, Wyeth Lederle Vaccines, Marietta, PA) was withdrawn from the US market <1 year after its introduction because of an increased risk of intussusception.^{1,2} Subsequent analyses estimated that 1 excess case of intussusception occurred among every 10 000 children vaccinated, and this risk primarily occurred in the first week after the first dose.³ Two new rotavirus vaccines were subsequently licensed and recommended for routine use in the United States. In 2006, a pentavalent bovine human reassortant vaccine (RotaTeq [RV5], Merck and Co, Whitehouse Station, NJ) was recommended with 3 oral doses given at 2, 4, and 6 months of age.⁴ In 2008, a monovalent vaccine based on an attenuated human rotavirus strain (Rotarix [RV1], GlaxoSmithKline Biologicals, Rixensart, Belgium) was also recommended with 2 oral doses given at 2 and 4 months of age.⁵ Both vaccines were shown to be highly efficacious and safe in clinical trials with no increased intussusception risk detected in the 42 days after all doses of RV5 combined or in the 31 days after all doses of RV1 combined.^{6,7} Early postmarketing studies in the United States did not detect an increased risk of intussusception after rotavirus vaccination.^{8–10} However, more recent US studies have identified a small increased risk of intussusception associated with both RV1 and RV5, mainly in the first week after the first dose of vaccine.^{11–13} An estimated 1 to 5 excess cases of intussusception occur per every 100 000 children vaccinated.

Although epidemiologic studies can document a temporal association of intussusception with vaccination, ecologic assessment of disease trends before and after vaccine implementation can help assess whether a temporal risk translates to more intussusception cases at a population level. An overall

population-level increase in intussusception hospitalizations in US infants was not detected in ecologic analysis during the period of RotaShield use, despite a substantially higher estimated risk of intussusception with RotaShield compared with current rotavirus vaccines.^{14–16} An analysis of a subset of infants enrolled in the RV1 clinical trial in Latin America showed a significantly reduced risk (relative risk: 0.28; 95% CI: 0.10–0.81) of intussusception among vaccine recipients compared with placebo recipients, suggesting that rotavirus vaccination may decrease the incidence of intussusception later in infancy, perhaps by protection from intussusception caused by wild-type rotavirus infection, but this hypothesis has not been explored at the population level.¹⁷

A previous study of US hospital discharge data found a small increased risk of intussusception hospitalizations among children 8 to 11 weeks of age in 2007 through 2009 compared with a prevaccine baseline from 2000 through 2005 but no sustained population level change in intussusception hospitalizations rates among all children <12 months of age.¹⁸ The objective of the current analysis is to update the previous analysis with 4 additional years of postvaccine introduction data from 2010 through 2013 to examine trends in intussusception hospitalization rates among all children <12 months of age as well as among children in the age groups during which doses of rotavirus vaccine are recommended.

METHODS

We conducted a retrospective analysis of intussusception hospitalizations among US children <12 months of age from 2000 through 2013 as part of a collaboration between the Centers for Disease Control and Prevention

and the Agency for Healthcare Research and Quality. Data were abstracted from the State Inpatient Databases (SID) maintained by the Healthcare Cost and Utilization Project (HCUP), which is sponsored by Agency for Healthcare Research and Quality.¹⁹ HCUP is a collection of health care databases that provides multistate, discharge-level health care data through a federal-state-industry partnership. SID captures all hospitalizations at community hospitals in participating states. For this analysis, an intussusception hospitalization was defined as a hospitalization with an *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code for intussusception (560.0) listed as a discharge diagnosis. The infant's age in weeks, state of hospital admission, whether abdominal surgery (defined as an *ICD-9-CM* procedure code of 45.0–48.9 or 54.0–54.2) was performed, and month and year of hospitalization were extracted from the discharge records.

As the number of states providing data to SID increased over the study period, we restricted our analysis to the 26 states that provided data to SID each year from 2000 through 2013 (Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, New Jersey, New York, North Carolina, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, West Virginia, and Wisconsin). These states comprise ~74% of the US birth cohort. Rates of intussusception hospitalization were calculated by using the National Center for Health Statistics' bridged-race postcensal population estimates for 2000 through 2013 for the 26 participating states.²⁰ Births were assumed to be evenly distributed throughout the year when calculating rates by age.

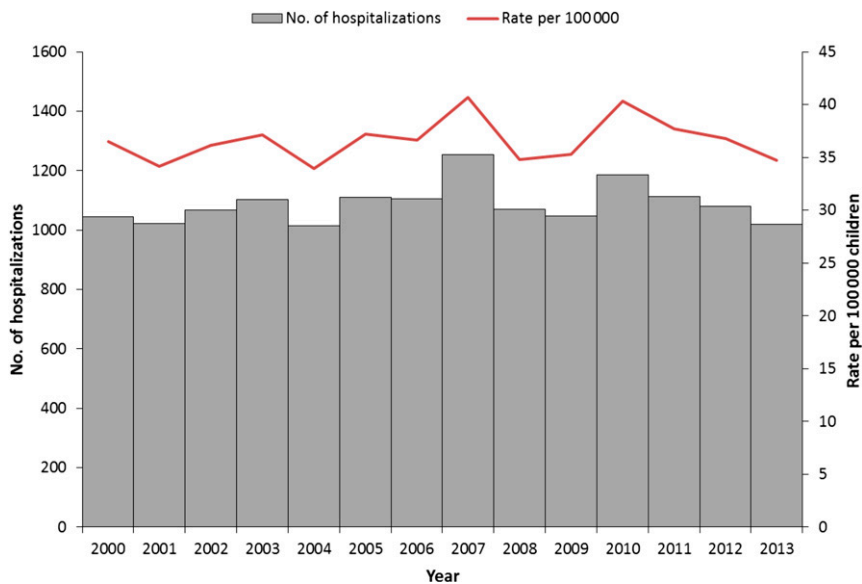


FIGURE 1

Trends in intussusception hospitalization among US children <12 months of age from 2000 through 2013. Data are from 26 states from the HCUP's SID¹⁵ and include the following states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Iowa, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, North Carolina, New Jersey, New York, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, Wisconsin, and West Virginia.

Trends over time in the number and rate of intussusception hospitalizations were examined from 2000 through 2013. Trends were further analyzed by age groups (6–14 weeks for the first dose, 15–24 weeks for the second dose, and 25–34 weeks for the third dose) based on the recommended age windows during which rotavirus vaccine doses are to be administered. Additionally, we examined intussusception hospitalization rates in children 8 to 11 weeks of age, when the majority of the first doses of rotavirus vaccine are administered.

To examine the relative difference in hospitalization rates for intussusception pre- and postrotavirus vaccine introduction, we compared the mean hospitalization rate for prevaccine years 2000 through 2005 with postvaccine introduction years 2007 through 2013. We excluded data from 2006 because rotavirus vaccine was introduced into the national immunization program during this year. We calculated rate ratios (RRs)

and 95% confidence intervals (CIs) by using Poisson regression analysis. Because all analyses were completed with aggregated and de-identified discharge records and no human subjects were involved, informed consent and bioethical review were not required.

RESULTS

We identified 15 231 intussusception hospitalizations among children <12 months of age that occurred in the 26 consistently reporting states over the 14-year study period from 2000 through 2013. Before rotavirus vaccine introduction in 2006, rates of intussusception were relatively constant over time, ranging from 33.9 per 100 000 children <12 months of age in 2004 to 37.2 per 100 000 children <12 months of age in 2003 and 2005 (Fig 1). In the postvaccine introduction era, rates of intussusception were significantly elevated in 2007 (40.7 per 100 000 children <12 months of age; RR: 1.13, 95% CI: 1.07–1.20) and in 2010 (40.3 per 100 000 children

<12 months of age; RR: 1.12, 95% CI: 1.06–1.20) but were not different from the prevaccine baseline in the other postvaccine introduction years (Table 1). There was no clear seasonality in intussusception hospitalization rates observed pre- or postvaccine introduction. The rate of surgery remained constant over the entire study period from 2000 through 2013 (range: 16.7–21.8 per 100 000) with ~50% of children requiring surgery. Deaths were rare (incidence of 0–3 per 1 000 000 children <12 months of age) with an average case fatality rate of 0.3%, ranging from 0% to 0.6%.

Trends in intussusception hospitalizations varied by the 3 defined age groups (Fig 2). Children 6 to 14 weeks of age had the lowest overall rates of intussusception hospitalization. In the prevaccine era from 2000 through 2005, the average rate of hospitalization was 15.0 per 100 000 children 6 to 14 weeks of age (range: 12.6–17.8 per 100 000; Fig 3a). In this same age group, the rate of intussusception hospitalization was significantly elevated in 5 postvaccine introduction years. Rates were elevated by 43% in 2007 (21.4 per 100 000; RR: 1.43, 95% CI: 1.16–1.76), 50% in 2008 (22.5 per 100 000; RR: 1.50, 95% CI: 1.22–1.83), 25% in 2009 (18.7 per 100 000; RR: 1.25, 95% CI: 1.00–1.56), 42% in 2010 (21.3 per 100 000; RR: 1.42, 95% CI: 1.15–1.75), and 42% in 2012 (21.4 per 100 000; RR: 1.42 (95% CI: 1.15–1.76) but no different from the prevaccine baseline in the remaining 2 postvaccine years (2011 and 2013; Table 1). Similarly, in the 8- to 11-week age group, the rate of intussusception hospitalization was significantly elevated in all years by 46% to 101% (range: 16.7–22.9 per 100 000 children 8–11 weeks of age) compared with the prevaccine baseline (11.4 per 100 000; range: 8.3–14.1 per 100 000) except in 2011 (15.0 per 100 000) and 2013 (14.7

TABLE 1 Intussusception Hospitalizations Rates per 100 000 and RRs and 95% CIs by Age Group in the Pre- (2000–2005) and Post- (2007–2013) Rotavirus Vaccine Introduction Years

Age Group	2000–2005		2007		2008		2009		2010		2011		2012		2013	
	Mean Rate (min, max)	Rate	RR (95% CI)	Rate	RR (95% CI)	Rate	RR (95% CI)	Rate	RR (95% CI)	Rate	RR (95% CI)	Rate	RR (95% CI)	Rate	RR (95% CI)	
<12 mo	35.9 (33.9, 37.2)	40.4	1.13 (1.07–1.20)	34.8	0.97 (0.91–1.04)	35.3	0.98 (0.92–1.05)	40.3	1.12 (1.06–1.20)	37.3	1.04 (0.98–1.11)	36.7	1.02 (0.96–1.09)	34.7	0.97 (0.91–1.04)	
6–14 wk	15.0 (12.6, 17.8)	21.4	1.43 (1.16–1.76)	22.5	1.50 (1.22–1.83)	18.7	1.25 (1.00–1.56)	21.3	1.42 (1.15–1.75)	17.9	1.19 (0.95–1.49)	21.4	1.42 (1.15–1.76)	17.0	1.13 (0.90–1.43)	
8–11 wk	11.4 (8.3, 14.1)	20.7	1.82 (1.32–2.51)	22.9	2.01 (1.48–2.74)	16.7	1.46 (1.03–2.09)	20.4	1.79 (1.29–2.49)	15.0	1.32 (0.91–1.91)	17.4	1.52 (1.07–2.16)	14.7	1.29 (0.88–1.87)	
15–24 wk	46.4 (38.2, 50.8)	47.1	1.01 (0.89–1.15)	43.3	0.93 (0.82–1.06)	42.1	0.91 (0.79–1.04)	55.0	1.18 (1.05–1.34)	50.2	1.08 (0.95–1.23)	41.8	0.90 (0.79–1.03)	45.5	0.98 (0.86–1.12)	
25–34 wk	55.8 (53.8, 59.1)	59.6	1.07 (0.95–1.20)	45.5	0.82 (0.72–0.93)	55.7	1.00 (0.89–1.12)	54.1	0.97 (0.86–1.10)	56.1	1.01 (0.89–1.13)	57.1	1.02 (0.91–1.15)	49.8	0.89 (0.79–1.01)	

Data are from 26 states from the HCUP's SID¹⁵ and include the following states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Iowa, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, North Carolina, New Jersey, New York, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, Wisconsin, and West Virginia.

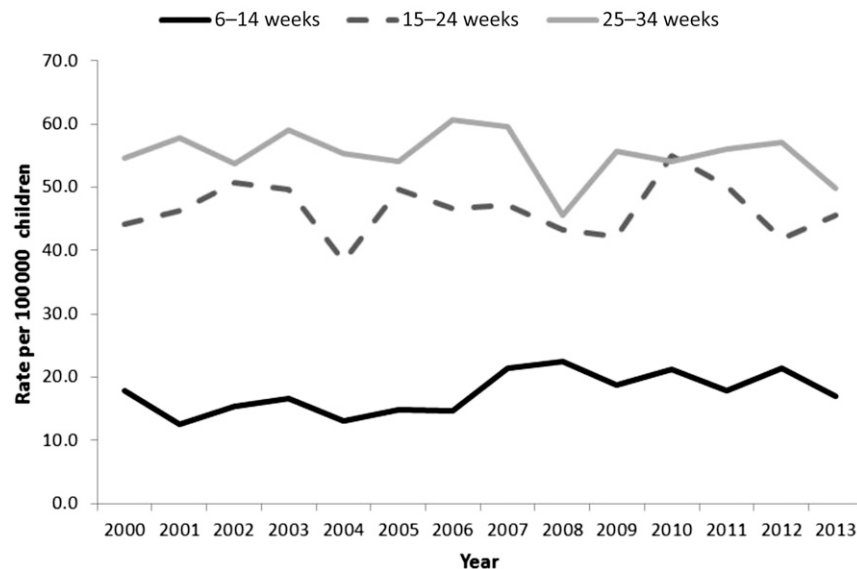


FIGURE 2

Trends in intussusception hospitalization rates from 2000 through 2013 by age group based on the recommended ages for rotavirus vaccine doses in the United States. Data are from 26 states from the HCUP's SID¹⁵ and include the following states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Iowa, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, North Carolina, New Jersey, New York, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, Wisconsin, and West Virginia.

per 100 000) when the rate was not significantly different from baseline (Fig 3b).

Among children 15 to 24 weeks and 25 to 34 weeks of age, when the second and third doses of rotavirus vaccine are usually administered, intussusception hospitalization rates pre- and postvaccine introduction were usually similar. For children 15 to 24 weeks of age, the rate of intussusception hospitalization was significantly elevated in 2010 (55.0 per 100 000 children 15 to 24 weeks of age; RR: 1.18, 95% CI: 1.05–1.34) compared with the prevaccine average of 46.4 per 100 000 but not significantly elevated in any other postvaccine introduction year. Among children 25 to 34 weeks of age, the rate of intussusception was significantly lower in 2008 (45.5 per 100 000 children 25 to 34 weeks of age; RR: 0.82, 95% CI: 0.72–0.93) compared with the prevaccine average of 55.6 per 100 000 and not significantly different from baseline rates in the remaining postvaccine introduction years.

In a subset of children 17 to 20 weeks of age when the majority of second doses are given, no increased risk of intussusception was observed (data not shown).

DISCUSSION

After rotavirus vaccine introduction in 2006, a consistent increase in the intussusception hospitalization rate among children 8 to 11 weeks of age, who receive the vast majority of first doses of rotavirus vaccine, was observed during all postvaccine years from 2007 through 2013 compared with the prevaccine baseline from 2000 through 2005, although statistical significance was not achieved in 2011 or 2013. This increased rate translates into an estimated 7 to 26 additional cases of intussusception in this age group annually. This observation is consistent with findings of a short-term temporal increased risk of intussusception in the first week after the first dose of rotavirus vaccine in 3 recent postlicensure studies in the

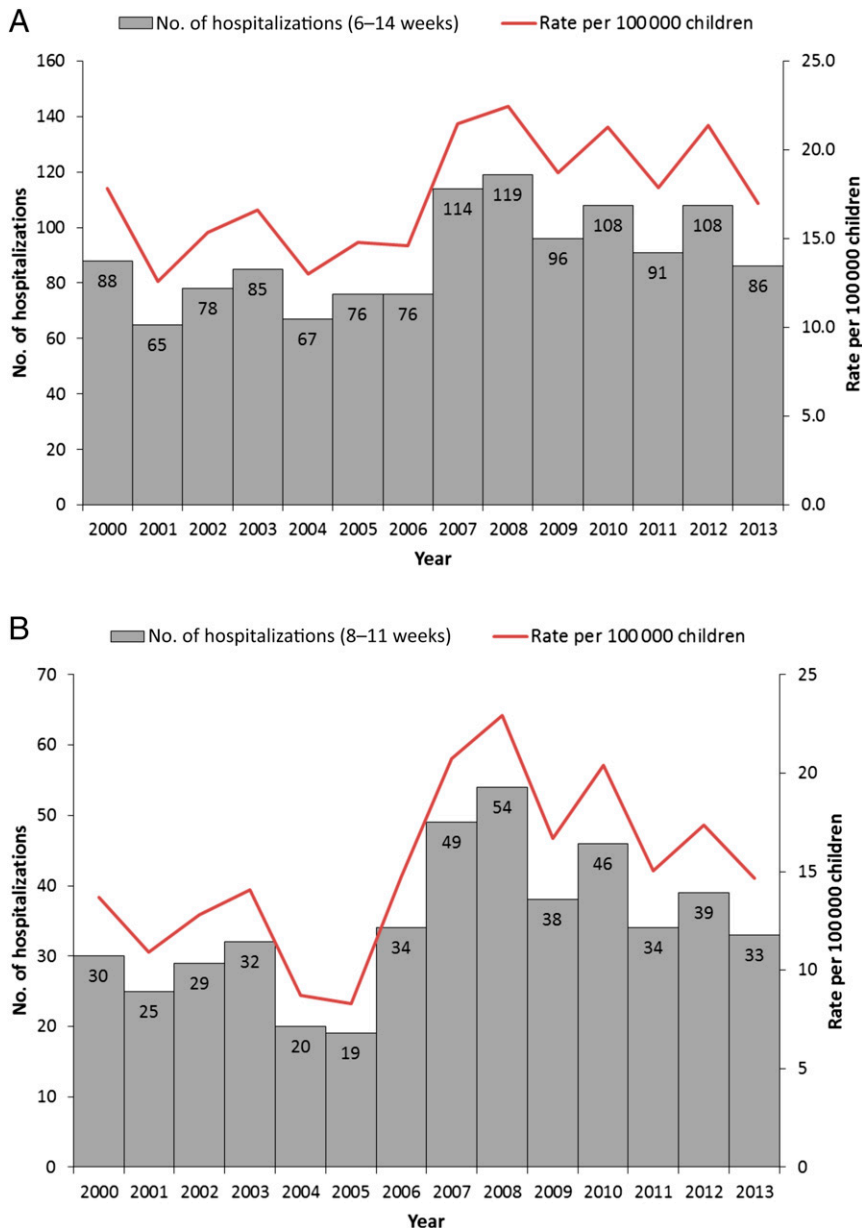


FIGURE 3

Trends in intussusception hospitalizations from 2000 through 2013 among (A) children 6 to 14 weeks of age and (B) children 8 to 11 weeks of age. Data are from 26 states from the HCUP's SID¹⁵ and include the following states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Iowa, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, North Carolina, New Jersey, New York, Oregon, South Carolina, Tennessee, Texas, Utah, Washington, Wisconsin, and West Virginia.

United States.^{11–13} However, given the comparatively low background rate of intussusception in children 8 to 11 weeks of age, no overall increased risk of intussusception was observed among all children <12 months of age, and no consistent change in the rate of intussusception hospitalization was observed in any of the older age groups.

Our analysis has several limitations. First, this is an ecologic analysis for which vaccination data are not available. Although rotavirus vaccination coverage among 19- to 35-month-olds in the United States has steadily increased from 44% in 2009% to 72% in 2014,²¹ the increased rates of intussusception hospitalizations among children

8 to 11 weeks of age cannot be linked directly to rotavirus vaccination because no information on vaccination status is captured in SID. However, this finding of increased intussusception risk in children aged 8 to 11 weeks but not in other age groups is consistent with other US studies that have been able to associate an increased risk of intussusception in the first week after the first dose of vaccine. Second, intussusception hospitalizations were defined using *ICD-9-CM* codes from a hospital discharge database, and no attempts were made to confirm the diagnosis. A retrospective study at 3 pediatric hospitals in the United States found that 89% of hospitalizations with an intussusception *ICD-9-CM* code meet the criteria for the highest level of diagnostic certainty for intussusception, and only 3% of identified intussusception cases that met this criteria did not receive the *ICD-9-CM* code for intussusception.²² Therefore, it is likely that the majority of intussusception hospitalizations from reporting hospitals in the 26 states was captured in this analysis. Third, the analysis was restricted to 26 states that continuously reported data from 2000 through 2013. Vaccine uptake and coverage has varied from state to state, but these 26 states are geographically dispersed and account for 74% of the US birth cohort and therefore are likely representative of the entire US birth cohort.

Finally, management practices for intussusception may have changed over the 14-year study period. Cases managed in outpatient settings, including short stay and emergency department care, will not have been captured by the database used in this analysis. In an analysis of a subset of states for which emergency department data were available, the proportion of intussusception cases treated in the emergency department versus hospitalized increased over time among all children <12 months

of age, but case numbers were too small to reliably examine by age group (data not shown). However, if emergency department care has increased in recent years, we may be underestimating the overall rate of intussusception in children in more recent years.

After introduction of rotavirus vaccines into the national immunization schedule in the United States, rates of rotavirus disease have declined sharply resulting in the prevention of >176 000 hospitalizations, 242 000 emergency department visits, and 1.1 million outpatient visits from 2007 to 2011.²³ In our ecological evaluation, a small increased risk of intussusception was observed in children 8 to 11 weeks of age when the majority of rotavirus vaccine doses are given, and this increase is consistent with a small increased risk of intussusception observed in the first week after the first dose in postmarketing studies. No overall increased risk of intussusception hospitalization was observed among all children <12 months of age, nor was a consistent change in the rate of intussusception hospitalization observed in any

of the older age groups. However, given the magnitude of the declines in rotavirus disease compared with the small increased risk of intussusception, the public health benefits of rotavirus vaccination far exceed the increased risk of intussusception.

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ABBREVIATIONS

CI: confidence interval
HCUP: Healthcare Cost and Utilization Project
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
RR: rate ratio
RV1: monovalent rotavirus vaccine
RV5: pentavalent rotavirus vaccine
SID: State Inpatient Databases

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