

Reduction in Acute Gastroenteritis Hospitalizations among US Children After Introduction of Rotavirus Vaccine: Analysis of Hospital Discharge Data from 18 US States

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Background. In 2006, RotaTeq (RV5) was recommended for routine vaccination of United States (US) infants. We compared hospitalization rates for acute gastroenteritis among US children aged <5 years during pre-RV5 rotavirus seasons from 2000 through 2006 with those during the post-RV5 2007 and 2008 seasons.

Methods. Using 100% hospital discharge data from 18 states, accounting for 49% of the US population, we calculated acute gastroenteritis hospitalization rates for children aged <5 years by rotavirus season, 8 age groups (0–2, 3–5, 6–11, 12–17, 18–23, 24–35, 36–47, and 48–59 months), and state.

Results. Compared with the median rate for the 2000–2006 rotavirus seasons (101.1 hospitalizations per 10,000 children), the rates for 2007 and 2008 (85.5 and 55.5 hospitalizations per 10,000 children) were 16% and 45% lower, respectively. Children aged 0–2 months had a 28% reduction, those aged 6–23 months had a reduction of 50%, and children aged 3–5 months and 24–59 months had reductions ranging between 42% and 45% during the 2008 rotavirus season, compared with the median rate for 2000–2006 rotavirus seasons.

Conclusions. The introduction of the RV5 vaccine was associated with a dramatic reduction in hospitalizations for acute gastroenteritis among US children during the 2008 rotavirus season.

In early 2006, a pentavalent rotavirus vaccine, RotaTeq (RV5), was licensed and subsequently recommended for use among infants in the United States [1]. RV5 was shown to be 96% effective in preventing severe rotavirus disease resulting in hospitalization during clinical trials [2]. RV5 is administered orally to infants at 2, 4, and 6 months of age with use of an age-restricted vaccination schedule because of insufficient data on the

safety and efficacy of RV5 among older infants [3]. Though not necessarily nationally representative of vaccine coverage in the United States, data from 6–8 population-based vaccination information system sentinel sites found that 1-dose RV5 coverage was 49% and that 3-dose coverage was 3% among age-eligible children during the 2007 rotavirus season [4]. During the 2008 season, more than one-half of eligible 3-month-old children had received at least 1 dose of RV5 and approximately one-third of age-eligible children had received 3 doses [4]. On the basis of these estimates, approximately one-third of children aged <2 years during the 2008 rotavirus season would have received at least 1 dose of rotavirus vaccine and, since catch-up vaccination is not allowed, only a very small proportion of children aged >2 years would have been vaccinated.

Despite the relatively modest estimates of RV5 coverage among United States (US) children, data from ~70 laboratories participating in the National Respiratory and Enteric Viruses Surveillance System illus-

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trated that the 2008 rotavirus season was substantially diminished, compared with previous seasons [5, 6]. In addition, active population-based surveillance data from 3 US counties (Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York) found that rotavirus hospitalization rates during the 2008 season were 80% lower, compared with the 2006 season [4]. However, to date, no studies have substantiated these findings with nationally representative acute gastroenteritis and rotavirus hospitalization rates for the United States.

In past years, the National Hospital Discharge Survey and, more recently, the Nationwide Inpatient Sample and Kids' Inpatient Database have been used to generate nationally representative hospitalization rates associated with acute gastroenteritis and rotavirus [7–10]. However, these comprehensive, annual survey databases are typically released 18 months after the close of the calendar year. Through an agreement between the Agency for Healthcare Research and Quality (AHRQ), 18 participating states in the Healthcare Cost and Utilization Project (HCUP), and the Centers for Disease Control and Prevention (CDC), data for ~100% of acute gastroenteritis hospitalizations occurring in short-stay hospitals through June 2008 in the 18 participating states were available for analysis in 2009. The combined populations of the 18 participating states that provided complete statewide hospitalization data account for 49% of children aged <5 years in the United States.

Using these extremely robust and timely hospitalization data, our objective was to describe hospitalization rates for acute gastroenteritis and rotavirus among children aged <5 years in the United States during January 2000 through June 2008. Our main focus was to compare hospitalization rates during the pre-RV5 licensure 2000–2006 rotavirus seasons with those for the post-RV5 licensure 2007 and 2008 seasons, to ascertain the potential impact of RV5 on acute gastroenteritis hospitalizations among young children.

METHODS

Data source. The HCUP within AHRQ began in 1988 with 8 participating states [11]. Since then, the number of participating states has increased to 40 states contributing hospitalization data in 2008 [12]. Full-year, state-level hospitalization data are sent to HCUP for standardization and then subsequently released to researchers [13]. The time between the close of a calendar year and the release of that year's state files and nationwide databases is between 6–12 months and 18 months, respectively. Consequently, for winter seasonal diseases, such as rotavirus, that end in the first one-half of a calendar year, this schedule results in a 12-month lag for state data and a 24-month lag for nationwide data between the end of a season and the availability of hospitalization data for analysis. In 2008, 18 HCUP state partners that were willing and able to provide

quarterly hospitalization data to AHRQ on an accelerated schedule were identified. These 18 HCUP state partners, AHRQ, and CDC entered into a novel agreement to conduct an assessment on a national scale of the 2008 rotavirus season hospitalization rates, compared with those for prior seasons.

Statewide quarterly hospitalization data from Arizona, California, Florida, Georgia, Hawaii, Indiana, Iowa, Kentucky, Maine, Maryland, Michigan, Minnesota, Missouri, Nevada, New York, South Carolina, Washington, and West Virginia were acquired for the 2008 rotavirus season (January through June 2008). Yearly intramural state files for the same participating states were analyzed for the previous rotavirus seasons. Because all hospitalization data was deidentified and provided in summary form, informed consent was not required for this study. All discharges from short-stay hospitals were used to identify acute gastroenteritis hospitalizations. Acute gastroenteritis hospitalizations were identified by using the *International Classification of Diseases, 9th Edition, Clinical Modification* (ICD-9-CM) codes for diarrhea of determined etiology (bacterial [001–005, excluding 003.2 and 008.0–008.5], parasitic [006–007, excluding 006.3–006.6], and viral [008.6 and 008.8]) and for diarrhea of undetermined etiology (presumed infectious [009.0–009.3] and presumed noninfectious [558.9 and 787.91]) [14]. Rotavirus hospitalizations were identified by using the rotavirus-specific ICD-9-CM code of 008.61. This code has been shown to be specific for identifying rotavirus laboratory-confirmed hospitalizations; however, rotavirus-coded events underestimate the true burden of rotavirus hospitalizations, because laboratory testing and coding for rotavirus are not routinely performed for all patients with gastroenteritis [15, 16]. Thus, in these analyses, monthly rates for rotavirus-coded hospitalizations are presented for children aged <5 years to illustrate the seasonal pattern. All other analyses focused on hospitalization rates for acute gastroenteritis.

Hospitalization rates. Hospitalization rates were calculated by dividing the number of hospitalizations by the number of children aged <5 years in each of the 18 participating states. Five states did not have continuous data through HCUP for the entire time period. These states (and years) for which data were unavailable are Indiana (2000–2002), Maine (2004–2005), Michigan (2000), Minnesota (2000), and Nevada (2000–2001). The denominators for calculating rates were adjusted accordingly to reflect these states being present or not for a given calendar year. Denominator data were obtained by using the National Center for Health Statistics' Bridged Race population estimates for 2000 through 2007 [17]. Because population data for 2008 was not available, the 2007 population data were used for calculating rates that included January through June 2008. Semiannual (January–June and July–December each calendar year), quarterly, and monthly hospitalization rates were calculated by age group (0–2, 3–5, 6–11, 12–17, 18–23, 24–35,

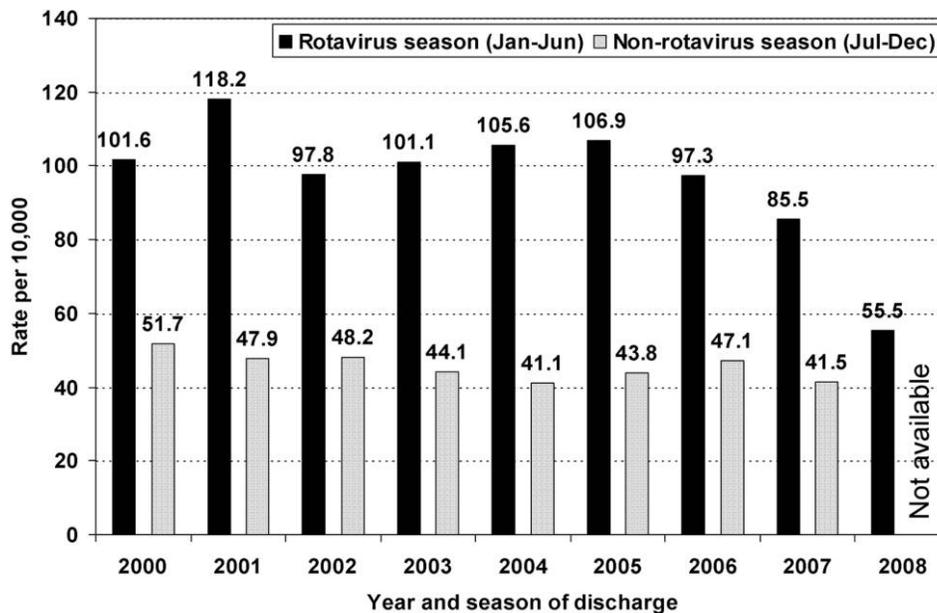


Figure 1. Acute gastroenteritis hospitalization rates by year and rotavirus season among children aged <5 years from January 2000 through June 2008, in 18 states.

36–47, and 48–59 months), sex, and state. A very small proportion of hospitalization records were missing information on sex (0.2%) or age in months (<0.01%). For records missing this information, these characteristics were imputed so that the records could be included in the analyses.

To compare the relative difference in pre- and post-vaccine licensure hospitalization rates for acute gastroenteritis, we compared the median hospitalization rate for January–June for calendar years 2000–2006 with that for January–June in calendar years 2007 and 2008. For this study, the calendar months of January through June were considered to be the rotavirus season for each calendar year, and the remaining months comprised the non-rotavirus seasons. Although there is year-to-year variability in the timing of rotavirus seasons, these calendar months capture most of the hospitalizations for acute gastroenteritis due to rotavirus [9, 15, 18, 19]. Statistical comparisons of rates were made using Poisson regression analysis [20]. Because of the large populations contributing to the rates (ie, state- and national-level populations), the width of 95% confidence intervals for rates were extremely narrow to the point of being noninformative. Consequently, the minimum and maximum rates for the pre-RV5 seasons were identified to better ascertain meaningful differences with the rates for the post-RV5 seasons. To obtain a nationally representative estimate of the reduction in acute gastroenteritis hospitalizations, we applied the median hospitalization rate for the 2000–2006 rotavirus seasons and the 2008 rate to the entire US population of children aged <5 years (assumed to be 20 million). These rates were used to extrapolate the annual number of acute

gastroenteritis hospitalizations (rounded to the nearest 100) occurring in the United States before and after vaccine licensure. Last, the average annual number of all-cause hospitalizations among children aged <5 years, excluding newborns, was obtained from the Nationwide Inpatient Sample for 2000–2006 [21].

RESULTS

Overall rates. During the 2000–2006 rotavirus seasons (January through June) across the 18 participating states, the median acute gastroenteritis hospitalization rate was 101.1 hospitalizations per 10,000 children, ranging from a low of 97.3 hospitalizations per 10,000 children in 2006 to a high of 118.2 hospitalizations per 10,000 children in 2001 (Figure 1). In 2007, the rate was 85.5 hospitalizations per 10,000 children, which was 16% lower ($P < .001$) than the 2000–2006 median rate. The rate for the 2008 season (55.5 hospitalizations per 10,000 children) was 46% lower ($P < .001$) than the 2000–2006 median rate. For the non-rotavirus seasons (July–December) during 2000–2007, the rate ranged between a low of 41.1 hospitalizations per 10,000 children in 2004 to 51.7 hospitalizations per 10,000 children in 2000 and did not show any discernible secular trends.

Rates by age group. For all age groups, hospitalization rates during the rotavirus seasons in 2007 and 2008 were below the median rate observed during the previous 7 rotavirus seasons during 2000–2006 (Figure 2). These observations were consistent by sex (data not shown). Relative to the median hospi-

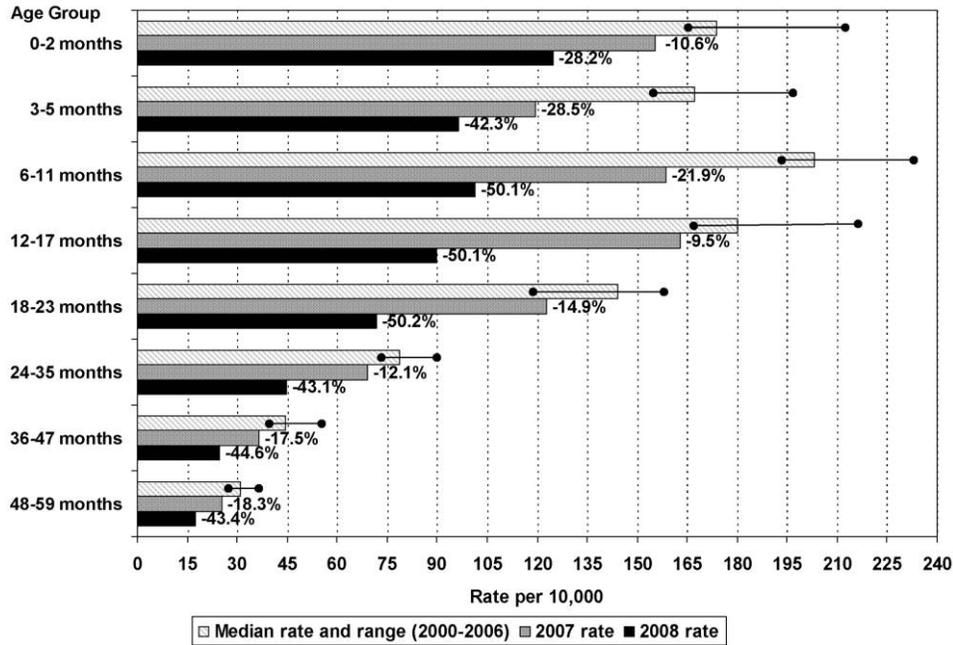


Figure 2. Acute gastroenteritis hospitalization rates by age group among children aged <5 years and relative change in rate during 2007 and 2008 rotavirus seasons, compared with median rate and range for 2000–2006 seasons, in 18 states. All decreases relative to the 2000–2006 median rate were statistically significant with $P < .001$.

talization rate from 2000 through 2006, the reduction in the 2007 hospitalization rates ranged between 9.5% among children aged 12–17 months to 28.5% among children aged 3–5 months (Figure 2). The reduction during the 2008 season was even more dramatic when the rate was compared with the median

rate for pre-RV5 seasons. Children aged 0–2 months had an almost 30% reduction, those aged 6–11, 12–17, and 18–23 months had 50% reductions, and the remaining age groups (3–5, 24–35, 36–47, and 48–59 months) had reductions ranging between 42% and 45%. During all of the rotavirus seasons prior

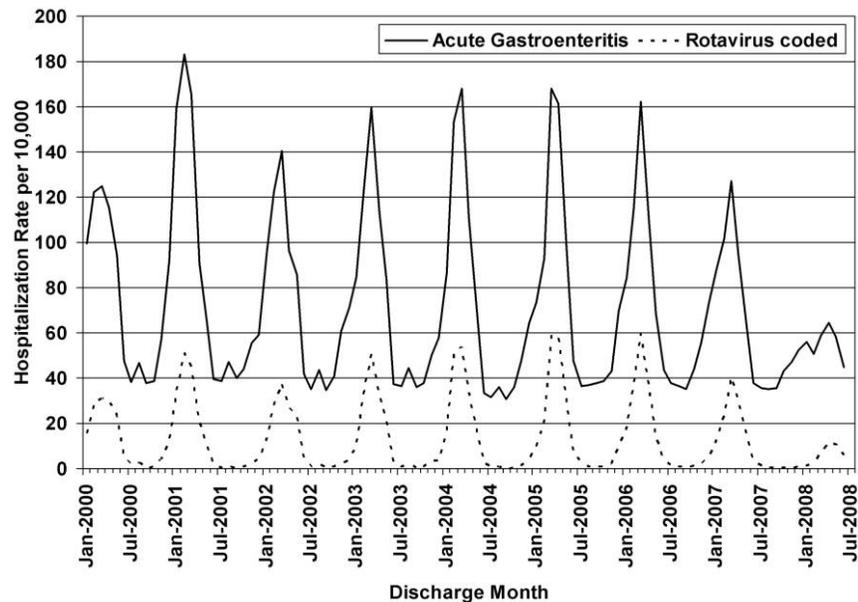


Figure 3. Monthly acute gastroenteritis and rotavirus *International Classification of Diseases, 9th Edition, Clinical Modification*-coded hospitalization rates among children aged <5 years from January 2000 through June 2008, in 18 states.

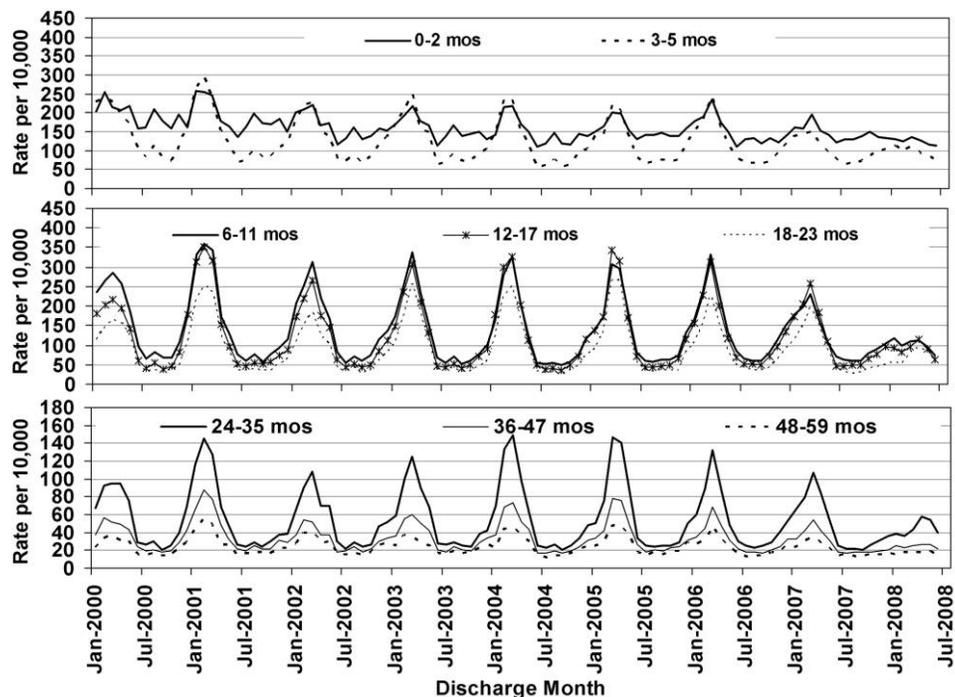


Figure 4. Monthly acute gastroenteritis hospitalization rates by age group for children aged <5 years from January 2000 through June 2008, in 18 states.

to RV5 introduction, children aged 6–11 months consistently had the highest hospitalization rates for acute gastroenteritis among all the age groups. In contrast, during the 2008 rotavirus season, children aged 0–2 months had the highest hospitalization rate.

Rates by month. During the prevaccine years from 2000 through 2006, hospitalization rates for acute gastroenteritis and for rotavirus specifically peaked annually during February or March (Figure 3). In contrast, the peak during the 2008 rotavirus season was not nearly as pronounced. For acute gastroenteritis hospitalizations, the 2008 season was bimodal, with a small peak occurring in January 2008 and a slightly higher second peak occurring in April 2008. The April 2008 peak rate of 64.5 hospitalizations per 10,000 children was approximately one-half to two-thirds lower than peaks during the 2000–2006 seasons. The diminished seasonal peak was also obvious for hospitalizations specifically coded for rotavirus during the 2008 season.

The diminished seasonal pattern in acute gastroenteritis hospitalization rates during the 2008 rotavirus season was observed for all age groups among children aged <5 years (Figure 4). In contrast to rates for older age groups, those for infants aged 0–2 months during the summer and fall months did not decrease as precipitously, resulting in a diminished trough between rotavirus seasons. As a result, the 2008 rotavirus season’s hospitalization rates for these children were roughly equal to those for the off-season months (ie, there was little or no peak).

In the pre-RV5 rotavirus seasons, the percentage of acute gastroenteritis hospitalizations specifically coded for rotavirus increased from 22% during the 2000 season to 29% during the 2006 season. The percentage observed for the 2007 season was 24%. During the 2008 rotavirus season, the percentage of acute gastroenteritis hospitalizations specifically coded for rotavirus decreased to only 12%.

Rates by state. Seasonal hospitalization rates of acute gastroenteritis varied substantially between states during the prevaccine seasons from January 2000 through June 2006. For example, Nevada demonstrated the lowest prevaccine seasonal rates with a median of 53.5 hospitalizations per 10,000 children aged <5 years, and West Virginia had the highest rates with a median of 189 hospitalizations per 10,000 children. In a similar manner, the seasonal decreases in acute gastroenteritis following use of the RV5 vaccine varied across the states. For example, in 2007 Georgia, Hawaii, and Iowa had acute gastroenteritis hospitalization rates that were >30% lower than those for prior seasons (Table 1). However, the remaining 15 states had relatively modest or no decrease in the 2007 rate, compared with rates for prior seasons. Most of the 18 states demonstrated a substantial decrease in hospitalization rates during the 2008 rotavirus season, including 9 that had decreases >50% and 6 that had decreases between 35% and 50%. However, during the 2008 season, the rates for Arizona and Nevada were higher than the median rate for pre-RV5 seasons.

National estimate of reduction. By applying the rates from

Table 1. Comparison of Median Rates of Hospitalization for Acute Gastroenteritis during the 2000–2006 Rotavirus Seasons (January–June) with Rates During the 2007 and 2008 Seasons among Children Aged <5 Years in 18 States

State	Period				
	2000–2006	2007		2008	
	Rate, median (minimum–maximum) hospitalizations per 10,000 children	Rate, hospitalizations per 10,000 children	Percent difference ^a	Rate, hospitalizations per 10,000 children	Percent difference ^a
Arizona	72.3 (59.8–80.2)	66.0	–8.7 ^b	84.6	17.1 ^d
California	80.8 (70.4–90.5)	62.2	–23.0 ^d	38.3	–52.7 ^d
Florida	142.1 (118.8–154.7)	113.0	–20.4 ^d	70.9	–50.1 ^d
Georgia	92.2 (89.1–101.2)	62.2	–32.5 ^d	37.7	–59.1 ^d
Hawaii	94.4 (71.9–122.1)	57.2	–39.4 ^d	53.5	–43.3 ^d
Iowa	117.5 (107.0–139.0)	67.6	–42.4 ^d	65.5	–44.3 ^d
Indiana	92.8 (63.5–100.7)	67.1	–27.7 ^d	41.4	–55.4 ^d
Kentucky	172.0 (142.7–215.2)	134.6	–21.7 ^d	76.1	–55.8 ^d
Maryland	88.5 (64.3–115.2)	73.1	–17.3 ^d	41.1	–53.6 ^d
Maine	79.5 (58.1–104.9)	57.7	–27.5 ^d	36.7	–53.8 ^d
Michigan	89.2 (75.1–120.9)	96.4	8.0 ^c	44.6	–50.0 ^d
Minnesota	122.6 (114.8–145.8)	112.8	–8.0 ^c	77.7	–36.6 ^d
Missouri	123.2 (107.8–132.9)	100.9	–18.1 ^d	76.5	–37.9 ^d
Nevada	53.5 (43.1–59.2)	49.2	–8.1	60.4	12.9
New York	126.0 (106.7–146.7)	118.4	–6.1 ^d	70.0	–44.5 ^d
South Carolina	143.5 (127.3–167.1)	114.4	–20.2 ^d	55.5	–61.3 ^d
Washington	70.7 (49.9–82.1)	61.1	–13.7 ^d	55.7	–21.3 ^d
West Virginia	189.0 (128.3–234.9)	193.5	2.4	98.6	–47.8 ^d

NOTE. Data for 2000–2007 were obtained from Agency for Healthcare Research and Quality; Center for Delivery, Organization, and Markets; Healthcare Cost and Utilization Project; and State Inpatient Databases. Quarterly data for 2008 were provided by 18 Healthcare Cost and Utilization Project state partners.

^a Compared with the median January through June hospitalization rates for 2000–2006.

^b $P = .01$ –.049.

^c $P = .001$ –.009.

^d $P < .001$.

our study to the entire US population of children aged <5 years, it was estimated that before the introduction of RV5, 97,300–118,200 (median, 101,600) acute gastroenteritis hospitalizations occurred each rotavirus season (January–June each calendar year) in the United States. In contrast, during 2008, there were an estimated 55,500 hospitalizations. Thus, following the introduction of RV5, we estimated that the decrease in acute gastroenteritis hospitalizations during the 2008 rotavirus season ranged between 41,800 and 62,700.

DISCUSSION

This study confirms on a national scale that the 2008 rotavirus season among children aged <5 years was dramatically reduced compared to pre-RV5 seasons. In 2007, the first season after introduction of RV5 in the United States, we observed a 16% decrease in acute gastroenteritis hospitalization rates, compared with rates in pre-RV5 seasons during 2000–2006, with the greatest decreases observed among vaccine-eligible children aged 3–11 months. More convincingly, in 2008 we demon-

strated a 45% decrease in acute gastroenteritis hospitalization rates relative to rates in pre-RV5 seasons. In 2008, acute gastroenteritis hospitalization rates decreased for all children aged <5 years, including those who were either too young or too old to be eligible for RV5 vaccination. Based on the observed decrease during the 2008 season, we estimated that ~55,000 acute gastroenteritis hospitalizations were prevented during the 2008 rotavirus season in the United States. A decrease of this magnitude would translate into the elimination of 1 in every 20 hospitalizations among US children aged <5 years.

Active surveillance has established that rotavirus accounts for ~50% of acute gastroenteritis hospitalizations during January through June among US children [22]. It was also found in the large prelicensure trial for RV5 that all-cause gastroenteritis hospitalizations were reduced by 59% [2]. The observed 45% decrease in acute gastroenteritis hospitalization rates during the 2008 US rotavirus season is consistent with these observations, assuming that RV5 vaccination prevented a large proportion of the 58,000–70,000 rotavirus hospitalizations es-

timated to occur each year in the United States [9]. Acute gastroenteritis hospitalization rates do exhibit year-to-year variability, but the reduction in 2008 well exceeded the range of this variability and was also accompanied by a change in the seasonal pattern of rotavirus, with a substantially delayed season onset and peak [9, 10, 23]. These findings, combined with the substantial decreases in acute gastroenteritis hospitalization rates noted among age groups that were too young or too old to be vaccinated with RV5, raise the possibility that vaccination of a proportion of the population could be conferring indirect benefits (ie, herd immunity) to nonvaccinated individuals through reduced viral transmission in the community [24].

Some limitations should be considered in interpreting our data. This study used data from 18 states to evaluate the 2008 rotavirus season in the United States. When considering state-specific hospitalization rates, it should be noted that, in contrast to the denominators used for our rates, hospitalizations were not necessarily restricted to residents of the 18 participating states. Furthermore, state-to-state or hospital-to-hospital variability in identifying a health encounter as a hospitalization rather than a short-stay encounter (eg, a hospital admission lasting <24 h) could explain some of the differences in acute gastroenteritis hospitalization rates by state. The data from the 18 participating states in this study represent all regions of the United States and account for almost 50% of the US population aged <5 years. Additionally, rather than being a sample of hospitalizations, our data represent ~100% of hospitalizations occurring in short-stay hospitals and our study population is comprised of all children aged <5 years in these states. Thus, though not specifically designed to generate nationally representative hospitalization rates, our data likely provide an accurate representation of acute gastroenteritis hospitalizations among children aged <5 years in the United States. Also, because the rotavirus-specific ICD-9-CM code incompletely captures all rotavirus hospitalizations, we relied on all-cause acute gastroenteritis hospitalizations to ascertain the impact of RV5. Although the distinct winter seasonal pattern of rotavirus and the high prevalence of rotavirus allows the use of acute gastroenteritis hospitalizations during the rotavirus season as a reasonable proxy, year-to-year variability in gastroenteritis caused by other pathogens with winter seasonality (eg, norovirus) could have had some impact on our findings [25, 26]. However, the seasonal pattern we observed for acute gastroenteritis hospitalization rates during the 2008 season was remarkably similar to that for rotavirus activity on the basis of national laboratory surveillance data which provide reassurance that the observed decreases were the result of diminished rotavirus activity [5, 6]. Finally, the consistency of the decrease in acute gastroenteritis hospitalization rates across most states and specifically during the rotavirus season strongly support that these changes resulted from RV5 vaccination, but the lack

of timely national data on RV5 coverage precluded correlation of the decreases with vaccine uptake. The National Immunization Survey provides national and state level estimates of vaccine coverage in the United States and relies on interviews that are restricted to households with children aged 19–35 months [27]. Consequently, there is a ~24 month lag between the introduction of a new vaccine for infants and the first robust national or state level estimates of vaccine coverage. It is noteworthy that 2 participating states, Arizona and Nevada, had 2008 rotavirus seasons that were similar to those in prior seasons. As data become available, it will be of interest to evaluate whether these 2 states had different patterns of RV5 coverage that could explain their distinct 2008 rotavirus seasons.

In conclusion, this study demonstrated on a multistate level that the introduction of the RV5 vaccine was associated with a dramatic reduction in hospitalizations for acute gastroenteritis among US children during the 2008 rotavirus season. The observed reductions in acute gastroenteritis hospitalizations exceeded what would be expected on the basis of vaccine coverage estimates and occurred in age groups not eligible for vaccination, raising the possibility of indirect benefits from vaccination. However, as surveillance data for only the first 2 seasons after RV5 introduction are available, it remains essential to continue monitoring acute gastroenteritis hospitalization rates during subsequent rotavirus seasons to fully understand and document the impact of RV5 as the vaccination program matures in the United States.

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