Direct and Indirect Effects of Rotavirus Vaccination Upon Childhood Hospitalizations in 3 US Counties, 2006–2009

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Background. Routine rotavirus vaccination of US infants began in 2006. We conducted active, population-based surveillance for rotavirus gastroenteritis hospitalizations in 3 US counties to assess vaccine impact.

Methods. Children <36 months old hospitalized with diarrhea and/or vomiting were enrolled from January through June each year during the period 2006–2009 and tested for rotavirus. Age-stratified rates of hospitalization for rotavirus infection were compared with corresponding vaccination coverage among a control group of children with acute respiratory illness. To assess direct and indirect benefits, vaccination coverage rates in the control group were multiplied by vaccine effectiveness estimates to calculate expected reductions in the rate of hospitalization for rotavirus infection. Rotavirus serotypes were compared across years.

Results. Compared with 2006, a significant reduction in rates of hospitalization for rotavirus infection ($P < .001$) was observed in 2008 among all age groups. There was an 87% reduction in the 6–11-month-old age group (coverage, 77%), a 96% reduction in the 12–23-months-old age group (coverage, 46%), and a 92% reduction in the 24–35-month-old age group (coverage, 1%), which exceeded reductions expected on the basis of coverage and vaccine effectiveness estimates. Age-specific rate reductions were nearly equivalent to those expected on the basis of age-specific vaccine coverage in 2009. Predominant strains varied annually: G1P[8] (91%) in 2006; G1P[8] (45%) and G12P[8] (36%) in 2007; G1P[8] (89%) in 2008; and G3P[8] (43%), G2P[4] (34%), and G9P[8] (27%) in 2009.

Conclusions. Rotavirus vaccination has dramatically decreased rates of hospitalization for rotavirus infection among children in these US counties. In 2008, reductions were prominent among both vaccine-eligible age groups and older, largely unvaccinated children; the latter likely resulted from indirect protection. Although rates among age groups eligible for vaccination remained low in 2009, indirect benefits disappeared.

Rotavirus is the major cause of severe acute gastroenteritis (AGE) in children. During the prevaccine era, rotavirus infected nearly every US child by 5 years of age, was estimated to be responsible for 4%–5% of all US pediatric hospitalizations [1], and accounted for ~50% of AGE hospitalizations during the winter months [2–4], with >$1 billion in annual US health care and societal costs [5, 6].

In February 2006, the US Advisory Committee on Immunization Practices (ACIP) recommended RotaTeq (Merck) for universal vaccination of US infants [7]. RotaTeq, a pentavalent (G1-4 P[8]) bovine–human, reassortant vaccine, is administered orally to infants at ages 2, 4, and 6 months [8]. A second rotavirus vaccine, Rotarix (GlaxoSmithKline Biologicals), was recommended by the ACIP in April 2008. Rotarix contains the attenuated monovalent G1 P[8] human rotavirus strain

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and is administered orally to infants at ages 2 and 4 months. Since 2006, the Centers for Disease Control and Prevention (CDC) New Vaccine Surveillance Network (NVSN) has conducted active, population-based surveillance for AGE in 3 US counties surrounding Cincinnati, Ohio; Nashville, Tennessee; and Rochester, New York.[2, 9] This report describes the impact of rotavirus vaccine introduction on hospitalizations for rotavirus infection and the indirect protective benefits from vaccination in NVSN populations.

METHODS

Surveillance Methods

Details of NVSN surveillance methods have been previously published [2, 9]. Surveillance sites included Cincinnati Children's Hospital Medical Center (Hamilton County, Ohio), Vanderbilt University Medical Center (Davidson County, Tennessee), and the University of Rochester Medical Center (Monroe County, New York) and are hereafter referred to as "Cincinnati," "Nashville," and "Rochester." Institutional review board approvals were obtained from the CDC and from each study site.

Children <3 years old and hospitalized with diarrhea (≥3 episodes within 24 h) and/or vomiting (≥1 episode within 24 h) who were residents of the 3 study counties and who had informed consent from a parent or guardian were enrolled. Children were ineligible if they had a reported history of noninfectious diarrhea or clinical immunodeficiency. Hospitalizations included subjects who were escalated to inpatient status after being originally enrolled in the outpatient or emergency department settings with the same illness.

Demographic, epidemiologic, and clinical information were collected for each enrolled child. Nearly all (99%) of the bulk stool samples were obtained within 7 days of the date of hospital admission for AGE symptoms. Specimens were tested for rotavirus antigen using a commercial enzyme immunoassay, Rotaclone (Meridian Bioscience), and serotype analysis was conducted by reverse-transcription polymerase chain reaction (RT-PCR) and nucleotide sequencing [2, 9].

Vaccination Coverage Estimates

We used a control group of children with acute respiratory illness (ARI) to estimate rotavirus vaccination coverage for children in the 3 surveillance counties. Provider-verified vaccination records were obtained for those children <3 years old who were residents of the 3 counties with medically-attended respiratory symptoms and/or fever at the same NVSN hospitals and during the same time period as the rotavirus surveillance. Vaccination coverage is defined here as ≥1 dose of verified rotavirus vaccine among control subjects with ARI.

Calculation of Hospitalization Rates

Prospective, population-based hospitalization rates for rotavirus infection were calculated from 1 January through 30 June for 4 consecutive years, 2006–2009. Surveillance hospitals captured >95% of resident pediatric hospitalizations within each county. Hospitalization rates were calculated using the weighted number of laboratory-confirmed rotavirus hospitalizations divided by the number of children within the age cohort in the county population, as determined by the year 2000 US Census. Weighting was performed to account for the number of surveillance days, the proportion of the eligible children enrolled, and the percentage of stool samples collected. The 95% confidence intervals (CIs) were determined by conducting 1000 bootstrap samples for each rate and using the resulting 2.5 and 97.5 percentiles as the lower and upper confidence intervals, respectively [2, 9–12]

Age-Specific Comparisons of Hospitalization Rates

We used the Kolmogorov–Smirnov nonparametric test ($P < .05$ was defined as statistically significant) to compare the distribution of rotavirus-positive cases by age across study years. Using 2006 as the baseline year, we calculated age-specific rate differences for 2007 through 2009. Rates were compared across years using 2-sided Student's t tests tests that incorporated the standard error resulting from the bootstrap samples for each rate. Statistical analyses were conducted using SAS software, version 9.1 (SAS Institute).

Estimation of Direct and Indirect Protective Effects Due to Vaccination

The rotavirus vaccine coverage estimates for ARI controls for 1, 2, and 3 doses for each year of surveillance were multiplied by the rotavirus vaccine effectiveness (VE) estimates calculated for the NVSN populations by dose [13]: 1 dose (VE, 73%; 95% CI, 43%–88%), 2 doses (VE, 88%; 95% CI, 68%–95%), and 3 doses (VE, 85%; 95% CI, 72%–91%). The resulting percentage was used as the expected reduction in rates of hospitalization for rotavirus infection due to the direct protective effect of the vaccine. The expected hospitalization rate reductions were compared with the observed NVSN hospitalization rate reductions for the corresponding years. Observed reductions exceeding the expected reductions were assumed to represent the indirect protective benefit gained from rotavirus vaccination, as well as the contribution of any secular variation.

RESULTS

NVSN Surveillance Enrollment

A total of 837 children <3 years old who were hospitalized with AGE were enrolled from January through June for 4 consecutive rotavirus seasons (2006–2009) at the 3 NVSN surveillance sites. Among another 109 children (11%) who were determined to be

eligible at screening but were not enrolled, reasons for non-enrollment included refusal of consent (36%), no English being spoken and translation services being unavailable (29%), no guardian being present (19%), and "other" reasons (15%). (Figure 1) Whole stool specimens were collected from 725 (87%) of the 837 enrolled children, of which 720 (99%) were tested for rotavirus. Nearly all (99%) of the bulk stool specimens were collected within 7 days of the date of hospital admission for AGE symptoms, and 96% were collected within 3 days (mean time to specimen collection, 0.5 days).

Overall, of the 720 specimens collected, 261 (36%) had test results that were positive for rotavirus. The numbers and proportions of specimens with test results positive for rotavirus, by study year, were 107 (51%), 101 (52%), 9 (6%), and 44 (26%) during 2006, 2007, 2008, and 2009, respectively. (Figure 2) Of these rotavirus-positive specimens, 103 were from Cincinnati, 59 were from Nashville, and 99 were from Rochester. Statistical significance ($P < .05$) was observed for differences between subjects with AGE who had test results negative for rotavirus and those with AGE who were rotavirus positive by surveillance site, age distribution, year of capture, race, ethnicity, and insurance status, but not by gender. Compared with rotavirus-positive subjects, control subjects with ARI were statistically different across all variables. (Table 1)

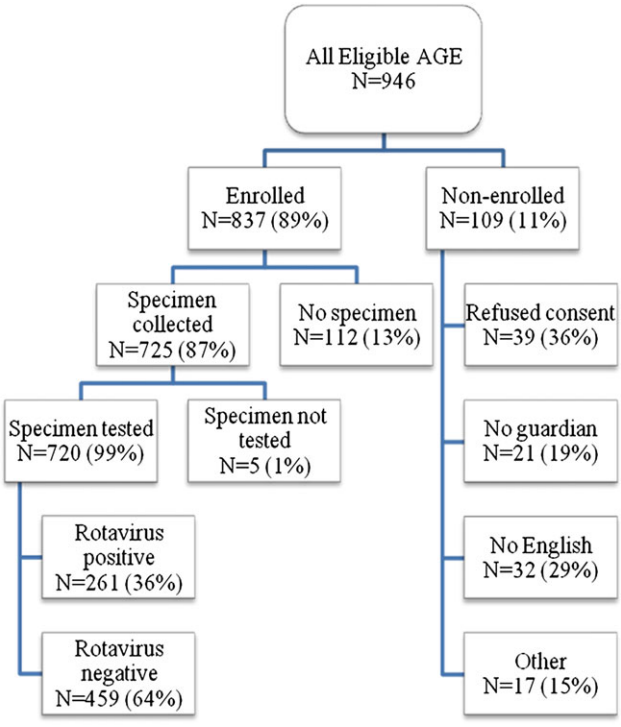

Figure 1. Flowchart describing New Vaccine Surveillance Network (NVSN) acute gastroenteritis (AGE) enrollment, specimen collection, rotavirus testing, and results, 2006–2009.

The median and mean (95% CI) ages of hospitalized, rotavirus-positive children <3 years old fluctuated yearly. (Figure 3) The proportion of children testing positive for rotavirus by age group changed over time, with over half (52%) of rotavirus cases occurring among children 24–35 months old in 2009, compared with previous proportions of 12%, 28%, and 11% in 2006, 2007, and 2008, respectively. (Figure 3)

Rotavirus Hospitalization Rates

NVSN rotavirus infection hospitalization rates were 22.5 hospitalizations per 10,000 children <3 years old (95% CI, 19.2–25.7) in 2006 [2] and 21.6 hospitalizations per 10,000 children (95% CI, 18.5–24.6) [9, 14] in 2007. In 2008, rotavirus infection hospitalization rates decreased dramatically across the NVSN surveillance sites, to 2.4 hospitalizations per 10,000 children (95% CI, 1.0–4.1), an 89% decrease, compared with the 2006 reference year. Decreases were observed at each site, including 89% in Cincinnati, 84% in Nashville, and 100% in Rochester. In 2009, the rotavirus infection hospitalization rate was 10.1 hospitalizations per 10,000 children (95% CI, 7.6–12.7), which was greater than the rate in 2008 but was still 55% lower than the baseline rate in 2006.

Rotavirus hospitalization rates during 2008 and 2009 were significantly lower than 2006 baseline rates for all children 0–35 months old ($P < .001$). Among 6-month age groups in 2009, children <6 months old and those 18–30 months old had significantly lower rotavirus infection hospitalization rates, compared with those for 2006 (statistical testing was not possible for ages 6–17 months in 2009 and for each specific age group in 2008 due to small sample sizes) (Table 2).

Compared with the reference year 2006 (when no rotavirus vaccination was reported for any surveillance subject), rotavirus infection hospitalization rates among infants 6–11 months old decreased 9%, 87%, and 88% in 2007, 2008, and 2009, respectively. Similarly, children 12–23 months old were hospitalized with rotavirus at rates that were 12%, 96%, and 75% lower

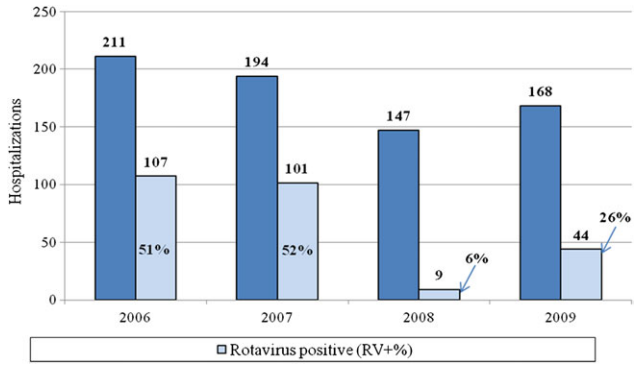

Figure 2. Number and proportion of New Vaccine Surveillance Network (NVSN) hospitalized children <3 years of age with acute gastroenteritis (AGE) who tested positive for rotavirus, by year.

Table 1. Characteristics of New Vaccine Surveillance Network (NVSN) Children <3 Years of Age Hospitalized With Acute Gastroenteritis (AGE) and Having a Stool Specimen Collected and Control Subjects With Acute Respiratory Virus Infection (ARI), January–June, 2006–2009

Characteristic	No. (%) subjects with AGE		P [a]	No. (%) of control subjects with ARI (n = 1964)	P [b]
	Rotavirus negative (n = 459)	Rotavirus positive (n = 261)			
Study subjects, % of total subjects	63.8	36.3			
Study site			<.001		<.001
Cincinnati	234 (51.0)	103 (39.5)		585 (29.8)	
Nashville	123 (26.8)	59 (22.6)		783 (39.9)	
Rochester	102 (22.2)	99 (37.9)		596 (30.4)	
Age, months			<.001		<.001
<6	203 (44.2)	44 (16.9)		1029 (52.4)	
6–11	82 (17.9)	36 (13.8)		295 (15.0)	
12–17	65 (14.2)	64 (24.5)		251 (12.8)	
18–23	44 (9.6)	52 (19.9)		178 (9.1)	
24–29	41 (8.9)	44 (16.9)		123 (6.3)	
30–35	24 (5.2)	21 (8.1)		88 (4.5)	
Year			<.001[c]		<.001[c]
2006	104 (22.7)	107 (41.0)		458 (23.3)	
2007	93 (20.3)	101 (38.7)		356 (18.1)	
2008	138 (30.1)	9 (3.5)		487 (24.8)	
2009	124 (27.0)	44 (16.9)		663 (33.8)	
Race			<.001[c]		<.001[c]
White	211 (46.0)	152 (58.2)		824 (42.0)	
Black	156 (34.0)	75 (28.7)		607 (30.9)	
Other	88 (19.2)	33 (12.6)		531 (27.0)	
Unknown	4 (0.9)	1 (0.4)		2 (0.1)	
Ethnicity			.045[c]		<.001[c]
Non-Hispanic	399 (86.9)	235 (90.0)		1621 (82.5)	
Hispanic	60 (13.1)	24 (9.2)		341 (17.4)	
Unknown	0 (0)	2 (0.8)		2 (0.1)	
Sex			.42		<.001
Male	228 (49.7)	121 (46.4)		1119 (57.0)	
Female	231 (50.3)	140 (53.6)		845 (43.0)	
Insurance			<.001[c]		<.001[c]
Public/mixed	287 (62.5)	116 (44.4)		1247 (63.5)	
Private Only	144 (31.4)	127 (48.7)		623 (31.7)	
Uninsured	28 (6.1)	17 (6.5)		84 (4.3)	
Unknown	0 (0)	1 (0.4)		10 (0.5)	

[a] P value for rotavirus-negative subjects versus rotavirus-positive subjects, by Pearson's χ^2 test.

[b] P value for control subjects with ARI versus rotavirus-positive subjects, by Pearson's χ^2 test.

[c] Fisher's exact test.

in 2007, 2008, and 2009, respectively, compared with rates in 2006 (Table 3). Decreases in these age groups were observed at each surveillance site and during each post-licensure year, except for Rochester in 2007. Many of the oldest children, those 24–35 months old, were too old to have been eligible to receive rotavirus vaccine, with none receiving vaccine in 2006 or 2007 and just 1% receiving vaccine in 2008 (Table 3). These older children exhibited the greatest variability in rates during the post-licensure period (Table 3) (Figure 1; online only).

Vaccination Coverage

Provider-verified vaccination records from 1964 control subjects with ARI were used to estimate rotavirus vaccine coverage in these populations, and 636 controls (32.4%) received at least 1 dose. The majority of subjects (95.1%) who were administered a rotavirus vaccination received only RotaTeq. Vaccination coverage (≥1 dose of verified rotavirus vaccine among controls with ARI) increased each surveillance year, with coverage rates of 0%, 10%, 42%, and 67% for 2006 through 2009, respectively

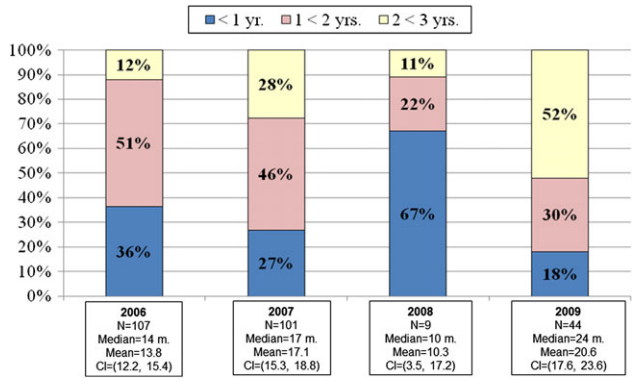

Figure 3. Age distributions for hospitalized rotavirus cases. Median ages and mean ages with 95% confidence intervals (CIs) are given in months for the period 2006–2009 among children <3 years old reported by the New Vaccine Surveillance Network (NVSN).

(Table 3). Specifically, among infants 6–11 months old, coverage was 0% in 2006, 30% in 2007, 77% in 2008, and 81% in 2009. Among children 12–23 years old, coverage was 0% in 2006, <1% in 2007, 46% in 2008, and 79% in 2009. Lastly, among children 24–35 months old, vaccine coverage was 0% in both 2006 and 2007, 1% in 2008, and 56% in 2009.

The uptake of rotavirus vaccination began slowly among Cincinnati infants (those 6–11 months old had 4% vaccine coverage), compared with coverage in Nashville (36% coverage) and Rochester (43% coverage) in 2007. By 2009, as this Cincinnati annual cohort aged, the coverage delay impacted children reaching 24–35 months of age, who had lower vaccine coverage (26%), compared with that for Nashville and Rochester (69% and 63%, respectively) (Table 3).

Among children hospitalized with rotavirus infection, none (0%) were vaccinated with a full course of either RotaTeq or Rotarix until 2009, when 6 (14%) of the children hospitalized with rotavirus infection had received 3 doses of RotaTeq.

Comparison of Observed Versus Expected Hospitalization Rates for Rotavirus Infection

NVSN vaccination coverage estimates were multiplied by the post-licensure estimates of rotavirus VE to determine the expected rotavirus infection hospitalization rate reductions that could be explained by the direct protective effect of vaccine, presented in Figure 4. In 2007, with ~14% of control subjects receiving ≥1 dose of rotavirus vaccine, the observed rotavirus infection hospitalization rate increased slightly, compared with 2006. For 2008, we compared the 73%, 88% and 85% NVSN vaccine effectiveness estimates for 1, 2, and 3 doses, respectively, with the 1-, 2-, and 3-dose vaccine coverage (equaling 7.3%, 12.5%, and 38.1%, respectively) to calculate an expected aggregate 49% decrease in the rate of hospitalizations for rotavirus infection. However, the actual, observed rate was 89% lower than the 2006 baseline rate. Age-specific analyses reveal that the disparity between observed and expected hospitalization rates was greatest among children 12–23 months of age, suggesting that this age group received substantial indirect protective benefit from vaccination in 2008 (Figure 2A–C; online only) Observed and expected rates then converged in 2009, suggesting that indirect protective benefits from vaccination ebbed (Figure 4) the same year that the median age of children hospitalized for rotavirus infection increased by 14 months.

Rotavirus Serotype Distributions

Figure 5 presents rotavirus serotype distributions among children hospitalized with rotavirus infection from 2006 through 2009. G1 P[8] (91%) was the predominant rotavirus serotype among hospitalized children in 2006. The emergence of G12 P[8] (36%) (at just 1 of the 3 surveillance sites) nearly overshadowed this G1 P[8] predominance (45%) in 2007. The prevalence of G12 P[8] was not sustained, however, in 2008, when G1 P[8] (89%) was again observed from the smaller sample of children hospitalized that year. A change toward G3

Table 2. Rotavirus Hospitalization Rates per 10000 Children and 95% Confidence Intervals, by 6-Month Age Group, 2006–2009

	Hospitalization rate, % (95% CI)			
Age, months	2006	2007	2008	2009
0–35	22.5 (19.2–25.7)	21.6 (18.5–24.6)	2.4[a] (1.0–4.1)	10.1[a] (7.6–12.7)
<6	28.4 (19.2–37.6)	14.5[b] (7.3–22.3)	7.2[c] (1.4–14.6)	8.3[a] (2.6–15.4)
6–11	20.5 (12.6–28.5)	18.7 (12.0–25.5)	2.7[c] (0.0–6.8)	2.5[c] (0.0–6.3)
12–17	42.5 (34.5–50.0)	33.6 (25.8–41.1)	0.0[c] (0.0–0.0)	6.7[c] (1.3–13.1)
18–23	25.9 (19.7–31.7)	26.7 (20.7–31.9)	3.0[c] (0.0–7.5)	10.5[a] (4.5–16.6)
24–29	10.0 (5.2–15.0)	26.5[a] (19.8–32.2)	1.4[c] (0.0–4.2)	19.9[b] (12.4–27.5)
30–35	7.1 (2.7–11.6)	9.3 (5.6–13.2)	0.0[c] (0.0–0.0)	12.2 (6.6–17.2)

[a] $P < .001$ when compared with the 2006 baseline rate for the age group.

[b] $.01 \leq P < .05$ when compared with the 2006 baseline rate for the age group.

[c] No comparison due to unweighted number of rotavirus cases ≤5 for the study period.

Table 3. Rotavirus Infection Hospitalization Rates and Rotavirus Vaccine Coverage During 2006–2009 by New Vaccine Surveillance Network Surveillance Sites and by 6-Month Age Groups

	Hospitalization rate per 10000[a] (% difference from 2006)							Vaccine coverage[b]		
Age, months	2006	2007		2008		2009		2007	2008	2009
All Sites										
6–11	20.5	18.7	(-8.8)	2.7	(-86.8)	2.5	(-87.8)	30.3	76.7	80.9
12–23	34.2	30.2	(-11.7)	1.5	(-95.6)	8.7	(-74.6)	0.4	46.4	78.6
24–35	8.6	17.9	(108.1)	0.7	(-91.9)	16.3	(89.5)	0.0	1.1	56.0
Cincinnati										
6–11	23.0	18.6	(-19.1)	6.7	(-70.9)	3.2	(-86.1)	4.0	69.8	73.0
12–23	39.4	18.9	(-52.0)	0.0	(-100)	3.3	(-91.6)	0.0	29.4	70.5
24–35	15.8	12.9	(-18.4)	1.8	(-88.6)	10.0	(-36.7)	0.0	1.7	25.6
Nashville										
6–11	20.6	6.7	(-67.5)	0.0	(-100)	0.0	(-100)	36.4	73.0	79.2
12–23	47.7	24.3	(-49.1)	5.5	(-88.5)	9.0	(-81.1)	0.0	54.6	82.0
24–35	2.2	7.3	(231.8)	0.0	(-100)	25.0	(1,036.4)	0.0	1.4	69.0
Rochester										
6–11	17.2	29.6	(72.1)	0.0	(-100)	3.8	(-77.9)	42.5	85.7	89.0
12–23	16.7	48.6	(191.0)	0.0	(-100)	14.9	(-10.8)	0.9	56.8	81.4
24–35	5.0	32.3	(546.0)	0.0	(-100)	16.8	(236.0)	0.0	0.0	63.0

NOTE. G12 P[8] rotavirus serotype accounted for 56% ($n = 25$) of all hospitalizations for rotatvirus infection in Rochester in 2007.

[a] Surveillance conducted January through June each surveillance year.

[b] The percentage of control subjects with acute respiratory infection who were administered ≥1 dose of rotavirus vaccine. Vaccine coverage data is provider verified. No doses were administered to surveillance subjects during 2006 season.

P[8] (43%) predominance was observed in 2009, with large proportions of specimens also identified as G2 P[4] (34%) and G9 P[8] (27%).

DISCUSSION

NVSN is the only multi-site, active, population-based rotavirus surveillance system in the US with prospective enrollment during both the pre- and postlicensure eras for rotavirus vaccine. Statistically significant reductions in hospitalizations for rotavirus infection were observed in 2008 and 2009 among age groups eligible for vaccination, validating that the introduction of rotavirus vaccination has led to dramatic reductions in rotavirus infection hospitalization rates among young children. These findings are supported by other US data sources, including the National Respiratory and Enteric Virus Surveillance System (NREVSS) and national medical claims databases. [15–19]

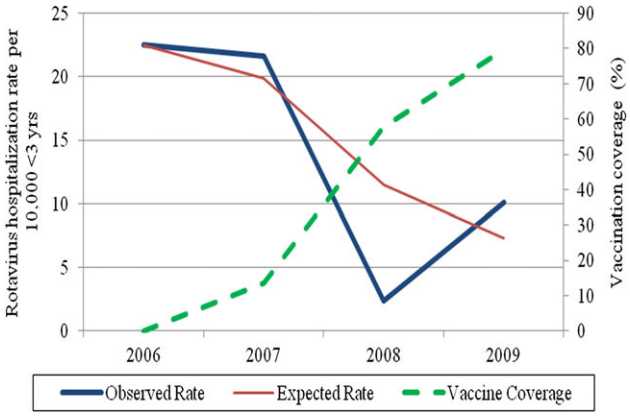

Figure 4. Observed New Vaccine Surveillance Network (NVSN) hospitalization rates, compared with those hospitalization rates that would be expected on the basis of NVSN vaccine effectiveness and NVSN vaccine coverage, 2006–2009.

Age-specific hospitalization rate reductions in 2008 exceeded those expected from direct vaccine coverage, even occurring among children who were too old to have been immunized. This observation was likely caused by disrupted rotavirus transmission among household and community contacts following the large increase in vaccination coverage in 2008, resulting in indirect protective benefits among unvaccinated children, as well, which is a phenomenon that was not studied in the clinical trials of either vaccine.

These indirect benefits were not observed in 2009, when rotavirus rates increased disproportionately among older children but still remained lower than the overall 2006 baseline year. The curtailed rotavirus transmission in 2008 may have allowed an unvaccinated segment of the childhood population to pass through the 2008 rotavirus season without exposure to wild-type virus. During the following 2009 rotavirus season, these children were 1 year older and still immunologically susceptible

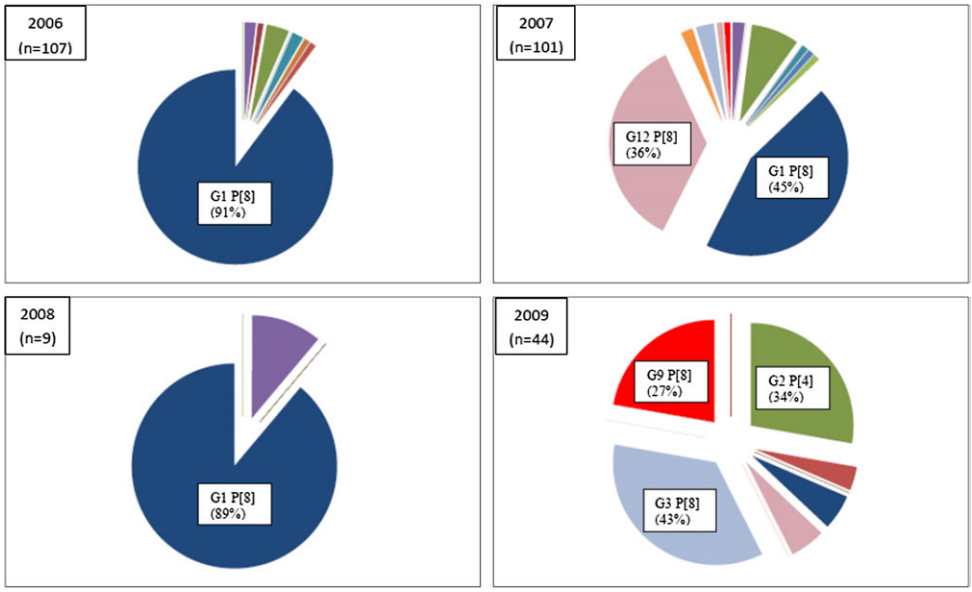

Figure 5. Predominant rotavirus serotypes among hospitalized children <3 years of age, New Vaccine Surveillance Network (NVSN), January–June, 2006–2009.

to rotavirus, resulting in increased risk for hospitalization due to rotavirus gastroenteritis. Although rotavirus infection hospitalization rates among age groups eligible for vaccination remained low in 2009, indirect protective benefits from vaccine disappeared, and the median age for rotavirus infection hospitalizations increased. These findings suggest that indirect protective benefits may have provided unvaccinated, older children a single-year deferral of exposure and subsequent infection with rotavirus gastroenteritis.

As indicated by our population-based data, the effects of rotavirus vaccination on household and community transmission will likely fluctuate as rotavirus-susceptible children accumulate and become infected. It is also possible that, although indirect benefits were not observed in 2009, these effects may reemerge in future years, even within specific communities. Furthermore, it is possible that, as high vaccine coverage is achieved, other age groups may continue to indirectly benefit from reduced rotavirus transmission, perhaps including infants too young to have yet been fully vaccinated and parents or caregivers of young children.

Our results do resemble those predicted by several mathematical modeling analyses designed to understand and forecast the effects of rotavirus vaccination upon disease trends. Using a deterministic, age-structured model with realistic age-mixing patterns in a developed-country setting, Atchinson et al [20] computed that short-term fluctuations—even changes in age distribution and age-specific rebounds in rotavirus incidence—were natural consequences of a rotavirus vaccination program in a developed country and did not necessarily indicate waning immunity or decreasing vaccine coverage. Models calculated by Pitzer et al [21] forecast that the mean age of severe rotavirus cases would increase with higher vaccine coverage because of delays in primary rotavirus infection, that the spatiotemporal characteristics of rotavirus infection epidemics are largely related to accumulations of fully susceptible individuals by geographic location, and that the reduction in rotavirus prevalence would be greater than that predicted by the direct effect of vaccination alone—all of which closely match our empirical observations.

In 2009, we observed a marked change from the previously predominant G1 P[8] strain toward G3 P[8] predominance across the surveillance system, consistent with other US findings [22]. Broad heterotypic immunity among those previously infected and those vaccinated would be expected to continue with G3 P[8] predominance, but further surveillance is warranted to evaluate whether this finding is simply secular variation or whether it is the result of a potential selection of rotavirus serotypes through vaccine pressures. The natural year-to-year variability in rotavirus incidence is difficult to quantify; however, we believe secular variation is evidenced by our observation of a rotavirus outbreak in 2007 related to an unusual serotype (G12 P[8]), which disproportionately affected hospitalization rates of certain age groups [9]. Such an occurrence would typically be masked in other datasets lacking population-based surveillance methods with laboratory confirmation and serotype characterization.

Our hospitalization surveillance of 3 US county childhood populations is not necessarily nationally representative. Results focus on the US experience with RotaTeq vaccine, because it was primarily used at our surveillance sites. However, ~4% of our

ARI control subjects had at least 1 dose of Rotarix. Although vaccination coverage estimates using control subjects with ARI are consistent within the equivalent county populations, clinical settings and time periods as our AGE surveillance data, vaccination histories from these control subjects may differ from those of children hospitalized with rotavirus infection. In particular, it is possible that control subjects with ARI who were hospitalized with certain vaccine-preventable respiratory diseases (eg, influenza and pneumococcal pneumonia) may also have been less likely to also receive rotavirus vaccine. Lastly, our calculation of the indirect protective benefits from vaccination was duplicated using VE estimates from children enrolled using a similar methodology at Texas Children's Hospital, Houston [23] (data not shown), and we found similar results.

In conclusion, our data confirm that the introduction of rotavirus vaccination among US children has dramatically decreased rates of hospitalization for rotavirus infection in NVSN childhood populations. The dramatic reductions observed in 2008 far exceeded what was expected on the basis of vaccine coverage and effectiveness and reductions among older, largely unvaccinated children in 2008 likely resulted from indirect protection conferred by younger, vaccinated children within the household and community. The convergence of the observed versus expected rates during 2009 and the shift in age distribution of cases of rotavirus infection suggests that indirect protective benefits disappeared the following year. Continued surveillance is needed to further elucidate the role of rotavirus vaccination coverage, indirect protective benefits, immunity over time, and serotypic variation upon rotavirus activity in the United States.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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