BRIEF REPORT

Infant Rotavirus Vaccination May Provide Indirect Protection to Older Children and Adults in the United States

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(See the editorial commentary by Glass, on pages 975–7.)

Following the introduction of rotavirus vaccination in the United States, rotavirus and cause-unspecified gastroenteritis discharges significantly decreased in 2008 in the 0–4, 5–14, and 15–24-year age groups, with significant reductions observed in March, the historic peak rotavirus month, in all age groups. We estimate that 15% of the total 66 000 averted hospitalizations and 20% of the $204 million in averted direct medical costs attributable to the vaccination program were among unvaccinated 5–24 year-olds. This study demonstrates a previously unrecognized burden of severe rotavirus in the population >5 years and the primacy of very young children in the transmission of rotavirus.

In 2006, routine vaccination of United States (US) infants with a pentavalent rotavirus vaccine (RV5) was recommended [1, 2]. By January 2008, coverage with ≥1 RV5 dose was an estimated 57% among <1-year-olds, 17% among 1-year-olds, and negligible among older children [3]. Postlicensure studies in US infants have confirmed the high effectiveness of RV5 seen in prelicensure trials [4], with a full course providing 85%–100% protection against rotavirus hospitalization [5, 6]. In 2008, rates of all-cause diarrhea hospitalizations among US children <5 years of age during the rotavirus season declined 46% [7]. The decline among children 3 months to 2 years of age who were age-eligible for vaccination exceeded the estimated vaccination coverage and declines were also seen in older, unvaccinated 2–4-year-olds, suggesting that rotavirus vaccination has also reduced transmission of wild virus, thereby providing indirect protection [7].

Using nationally representative data and time series regression techniques, we further assessed direct and indirect benefits from rotavirus vaccination among children >5 years, adults, and the elderly, among whom the burden of rotavirus hospitalizations has not been well documented.

METHODS. The Nationwide Inpatient Sample (NIS) is a nationally representative database of US hospital inpatient stays collected from a national sample of more than 1000 hospitals in 42 states [8]. Approximately 20% of all US hospitals are captured in the sample. We analyzed records with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9CM) code for rotavirus and cause-unspecified gastroenteritis-associated hospital discharges from 2000 to 2008. A rotavirus-coded discharge was defined as a record with the rotavirus code (008.61) in any coding position; a cause-unspecified gastroenteritis discharge was defined as a record with a nonspecific gastroenteritis code (009.0–009.3, 558.9, 787.91, 008.8) in any of the first 3 coding positions, with no specific gastroenteritis pathogen code in any other position.

Data were analyzed as a time-series of monthly counts of diarrheal hospitalizations that were either rotavirus-specific or cause-unspecified. We fitted time-series adapted regression models separately for each of 5 age groups. Poisson regression models were fitted, controlling for seasonal variation (using a month indicator) and secular trends (using a sequential numeric variable for year of study, thereby assuming a linear change over time). The standard error of the rate ratio was scaled to the Pearson χ^2 statistic divided by the residual degrees of freedom to account for overdispersion of the monthly counts [9]. Controlling for secular trends was crucial because there has been an increase in the rate of gastroenteritis admission in adults and elderly over the last decade [10]. A variable indicating postvaccine era was used to determine the relative rate (RR) in 2008 compared with the prevaccine era (2000–2006); 2007 was excluded as this was a transition year when coverage was increasing and vaccine impact was modest [7, 11, 12]. Deviance residuals of all models were inspected and in some models there was evidence of remaining autocorrelation. All the models were refitted including a 1- and 2-month lagged deviance variable; this did improve fit in some age groups (likelihood ratio test, $P < .05$) but in no models did the rate ratio coefficient of interest (2008 compared with previous years) change appreciably

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(by >0.1), so the presented results are from models without autocorrelation structure.

Subsequently, models were fitted separately by month, race, US Census region, and sex, for each age group, to determine if indirect vaccine impact differed by these characteristics. Averted admissions were estimated by multiplying the RR by the mean discharges in the prevaccine era (2000–2006) in age categories where statistically significant ($P < .05$) reductions were observed. To estimate the cost savings, averted discharges were multiplied by median hospital charges by age group for rotavirus hospitalizations in 2008. The NIS dataset reports hospital charges, which exceed actual costs. In order to estimate costs, we then multiplied by the cost to charge ratio. The 95% confidence intervals for admissions, bed-days and costs averted were generated by 10 000 Monte Carlo simulations, assuming normal distribution of the RRs and log-normal distributions of costs and bed-days.

RESULTS. In the 0–4 and 5–14-year age groups, there were markedly fewer rotavirus-coded and cause-unspecified gastroenteritis discharges in 2008 compared with the prevaccine annual minimum (Table 1). There was also a secular increase in rotavirus-coded discharges in age groups ≥15 years and among all age groups for cause-unspecified gastroenteritis discharges (Table 1; Figure 1). Therefore, in all subsequent results, regression models were used to control for these secular trends.

Rotavirus-coded hospital discharges decreased in 2008 in all age groups, with statistically significant reductions in the 0–4, 5–14, and 15–24-year age groups (RR = 0.22, 0.29, and 0.35, respectively; $P < .0001$ for all; Table 1; Figure 1*A–E*). In these same age groups, statistically significant reductions in cause-unspecified gastroenteritis discharges (RR = 0.61, 0.71, 0.92; $P < .0001$, $P < .0001$, $P = .01$, respectively) also occurred (Figure 1*F–J*). We estimate a total of 66 030 gastroenteritis hospitalizations averted (26 389 rotavirus-coded and 39 642 cause-unspecified) in 2008 in <25-year-olds, 10 220 (15%) of which were in the 5–24-year age group. In total, we estimate approximately 204 million (2008) dollars in averted hospitalization costs with 21% of these costs in the 5–24-year age group, due to their higher charges per hospitalization.

The reduction in cause-unspecified gastroenteritis discharges was focused in the late winter/early spring (Figure 2*F–J*), with the greatest reduction in March, in all child (RR = 0.30, $P < .0001$ in 0–4 years; RR = 0.44, $P < .0001$ in 5–14 years), adolescent/young adult (RR = 0.76, $P = .0006$ in 15–24 years), adult (RR = 0.88, $P = .09$ in 25–64 years), and elderly (RR = 0.89, $P = .003$ in ≥65 years) age groups.

The patterns of age-specific disease reduction were consistent between males and females and across regions (Table 2). However, the reductions were most pronounced in Hispanics with significant reductions across all age groups (RR = 0.66, $P < .001$), which was significantly greater than the impact in whites ($\chi^2 = 33.5$, 1 degree of freedom, $P < .001$ controlling for age).

DISCUSSION. Our findings suggest that, in 2008, vaccination of US infants against rotavirus provided indirect protection to older children and adults. Both rotavirus-coded and cause-unspecified gastroenteritis discharges were significantly reduced in age groups 3–24 years that were not eligible for vaccination, with the greatest reduction during March, the peak month of rotavirus activity in the prevaccine era. While overall annual discharges were not significantly reduced in age groups ≥25 years, in March significant reductions occurred in rotavirus-coded discharges in these age groups and also in cause-unspecified gastroenteritis discharges in the elderly. These indirect impacts are substantial: about 15% of the averted approximately 66 000 gastroenteritis hospitalizations occurred in the 5–14 and 15–24-year age groups, equating to a 25% and 7% reduction in gastroenteritis discharges in these age groups, respectively.

Indirect benefits were seen across all demographic strata but were most pronounced in Hispanics. There are 2 possible explanations for this observation. First, if Hispanic children had higher vaccine coverage, they might also gain greater indirect protection. However, data on rotavirus and other routine child immunizations indicate that Hispanic children have coverage similar to that of other races [13]. Furthermore, the direct impact of vaccination in children under the age of 3 was similar in Hispanics and white populations [14]. An alternative explanation is that exposure of older children and adults to infected infants is different among Hispanics compared with other groups in the United States, so protecting infants through vaccination has larger indirect effects. Supporting this hypothesis are the facts that Hispanics live in larger households (average 3.62 persons compared with 2.59 for the US population) and that Hispanic households are more likely to include children (52% compared with 33%) [15]. These data are consistent with a transmission mechanism whereby young children acquire their infections outside the household, and older children and adults acquire their infections from infected children within their household [16].

Using a related dataset but different methodology, Curns et al estimated a 45% reduction in all-cause gastroenteritis hospitalizations in US children <5 years, or approximately 55 000 hospitalizations averted, very similar to our estimate for this age group [7]. Data from one Australian state indicated a reduction in rotavirus hospitalizations by 50%–60% up to age 20 and in gastroenteritis admissions up to age 5 by 40% in 2008, the second year of substantial coverage in that country's rotavirus vaccination program [17]. Our study supports and extends these observations by demonstrating an impact in older children and adults, while using appropriate regression models that control for background seasonal and secular trends. Importantly, we observed a reduction in cause-unspecified hospitalizations, not

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Table 1. Cause-Unspecified Diarrheal Hospitalizations and Rotavirus-Coded Hospitalizations in 2008 Compared With the Prevaccine Era (2000–2006) in the United States, Including Estimated Hospitalizations, Bed-Days, and Costs Averted, Attributable to the Rotavirus Vaccine Program

	Cause-unspecified discharges				Rotavirus discharges						Total		
Age (years)	Median 2000–2006 (minimum)	2008	RR (95% CI)[a]	Admissions averted,[b] thousands (95% CI)	Median 2000–2006 (minimum)	2008	RR (95% CI)[a]	Admissions averted,[b] thousands (95% CI)	Median costs (2008 USD)[d]	Median length of stay (days)	Admissions averted,[b] thousands (95% CI)	Bed-days averted,[c] thousands (95% CI)	Costs averted, 2008, USD, millions[d] (95% CI)
0–4	78 930 (75 924)	50 519	0.61 (.52–.71)	30.8 (22.8–37.6)	32 086[f] (23 548)	9852	0.22 (.14–.34)	25.0 (21.4–27.6)	2897	2	55.8 (47.4–63.2)	128 (112–144)	162 (147–212)
5–14	24 946 (23 179)	17 884	0.71 (.65–.78)	7.2 (5.4–8.8)	1801[f] (1274)	747	0.29 (.19–.45)	1.28 (.99–1.46)	3750	2	8.51 (6.67–10.1)	19.6 (16.8–25.8)	32 (29–49)
15–24	20 306[f] (18 073)	21 769	0.92 (.86–.98)	1.6 (.36–2.7)	127[f] (81)	70	0.35 (.15–.82)	0.08 (.023–.108)	5925	2	1.70 (.46–2.80)	5.4 (1.6–9.4)	10 (3.2–28)
25–64[e]	146 000[f] (132 729)	174 565	0.99 (.95–1.03)		288[f] (231)	279	0.74 (.47–1.16)		7481	3			
≥65	118 332[f] (108 917)	147 906	1.03 (.96–1.1)		266[f] (168)	390	0.79 (.49–1.26)		10260	4			
All ages				39.6 (28.5–49.1)				26.4 (22.4–29.2)			66.0 (54.1–76.1)	153 (129–179)	204 (177–289)

Abbreviations: CI, confidence interval; RR, relative rate; USD, US dollars.

[a] All models controlling for secular and seasonal variation.

[b] Averted admissions were estimated by multiplying the rate ratio by the mean discharges in the prevaccine era (2000–2006) in age categories where statistically significant ($P < .05$) reductions were observed in 2008.

[c] To estimate averted bed-days, the averted hospitalizations were multiplied by mean length of stay for rotavirus hospitalizations in 2008 as reported in the Nationwide Inpatient Sample (NIS) dataset.

[d] To estimate averted costs, the averted hospitalizations were multiplied by mean hospital charges for rotavirus hospitalizations in 2008. The NIS dataset reports hospital charges, which exceed actual costs. In order to present costs, we then multiplied by the cost-to-charge ratio. Costs for rotavirus hospitalization have remained essentially unchanged from 2004 (median costs $2962) to 2008 (median costs $2897).

[e] We hypothesized that indirect protection may be afforded to adults of child-bearing age, so smaller age groups were initially considered. Preliminary analysis demonstrated no clear effect in 10-year age bands in adults, so to maximize statistical power the 25–64-year-old population was combined.

[f] Significant increasing trend during prevaccine period ($P < .1$).

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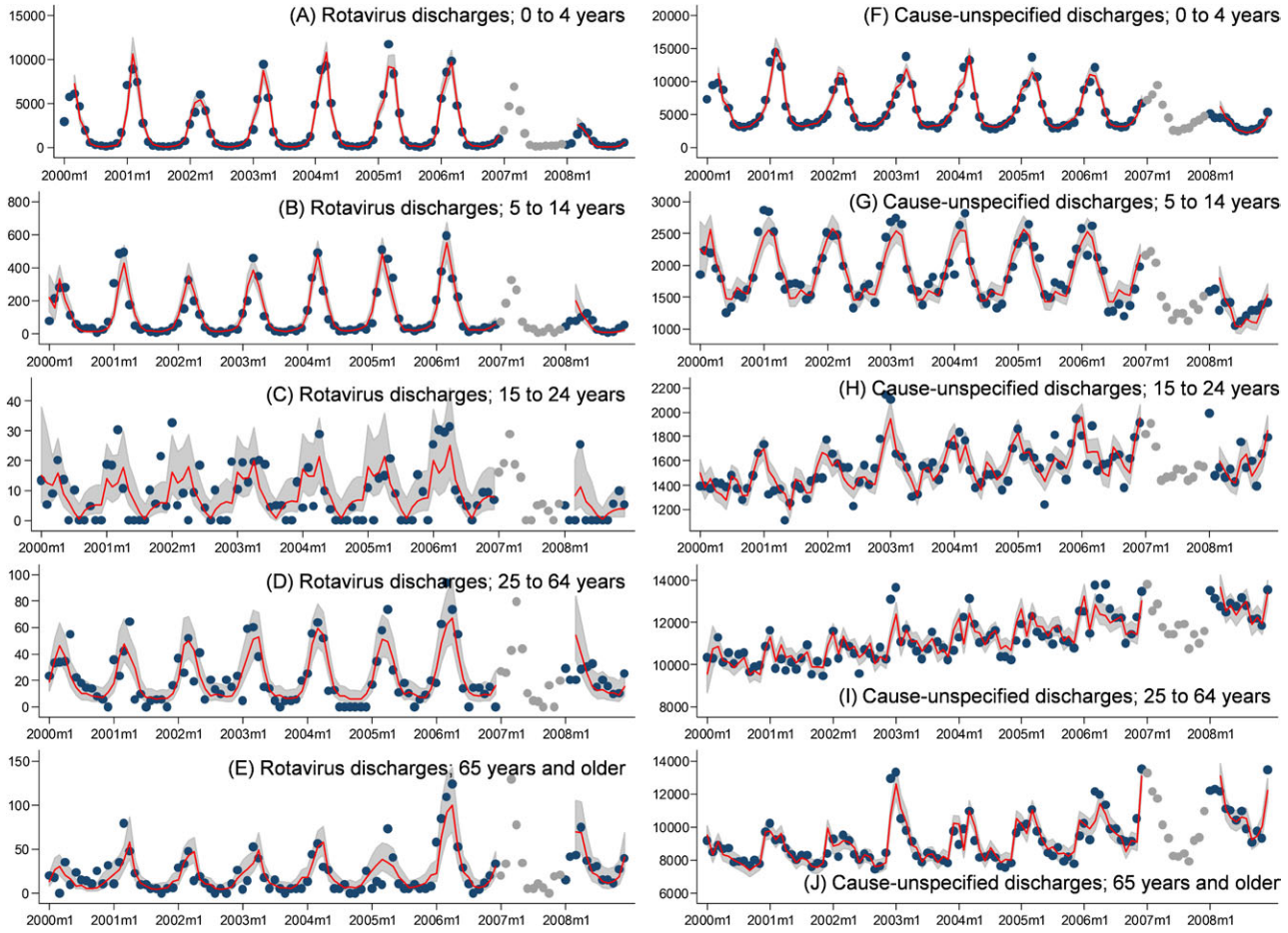

Figure 1. Observed and model-predicted monthly rotavirus discharges (*A*–*E*) and cause-unspecified discharges (*F*–*J*), 2000–2008. Dots represent observed discharges; red lines and gray-shaded areas represent model-predicted discharges and 95% confidence intervals, respectively. Models control for seasonal and secular trends. Because 2007 was a transitional year in terms of vaccine uptake, data from this year did not contribute to model fitting; 2007 is represented as gray dots.

only those rotavirus-coded, since the validity of the rotavirus ICD9-CM code in age groups outside children <5 years is not known. It is also crucial to note that there is annual variability in the size of the rotavirus season. It remains a possibility that at least some of the observed decrease in 2008 may be due to a small rotavirus year, independent of vaccination effect, so it will be important to monitor whether these signals of indirect protection continue in subsequent years. Other studies have demonstrated a shift to a later seasonal peak following vaccination in the United States and elsewhere [11, 18]. Although we detected a decrease in discharges during the historic rotavirus season, we did not detect significant increases in the summer months of 2008 in any age groups.

The cost-effectiveness study that supported the introduction of rotavirus vaccination in the United States estimated the national costs of rotavirus-associated hospitalization at approximately $200 million and projected potential cost savings in terms of hospitalizations averted at approximately $130 million [19]. We have estimated substantially larger cost savings because we have detected averted hospitalizations in unvaccinated groups including older children and adults, a benefit that was not foreseen and therefore not included in previous analyses. As the proportion of severe rotavirus disease treated in outpatient settings may be greater in older children and adults than in young children, future analysis should determine indirect impacts on emergency room visits, outpatient consultation, and community disease for gastroenteritis in older children and adults, and, if detected, be included in economic analyses that consider societal costs.

In conclusion, this study indicates a larger than previously recognized burden of rotavirus in older children and adults, and suggests that vaccination of infants, who are key to sustaining community transmission, could indirectly prevent this burden. The enhanced indirect protection seen in Hispanic populations is encouraging regarding the potential impact in settings where there are larger average household sizes. Live oral rotavirus

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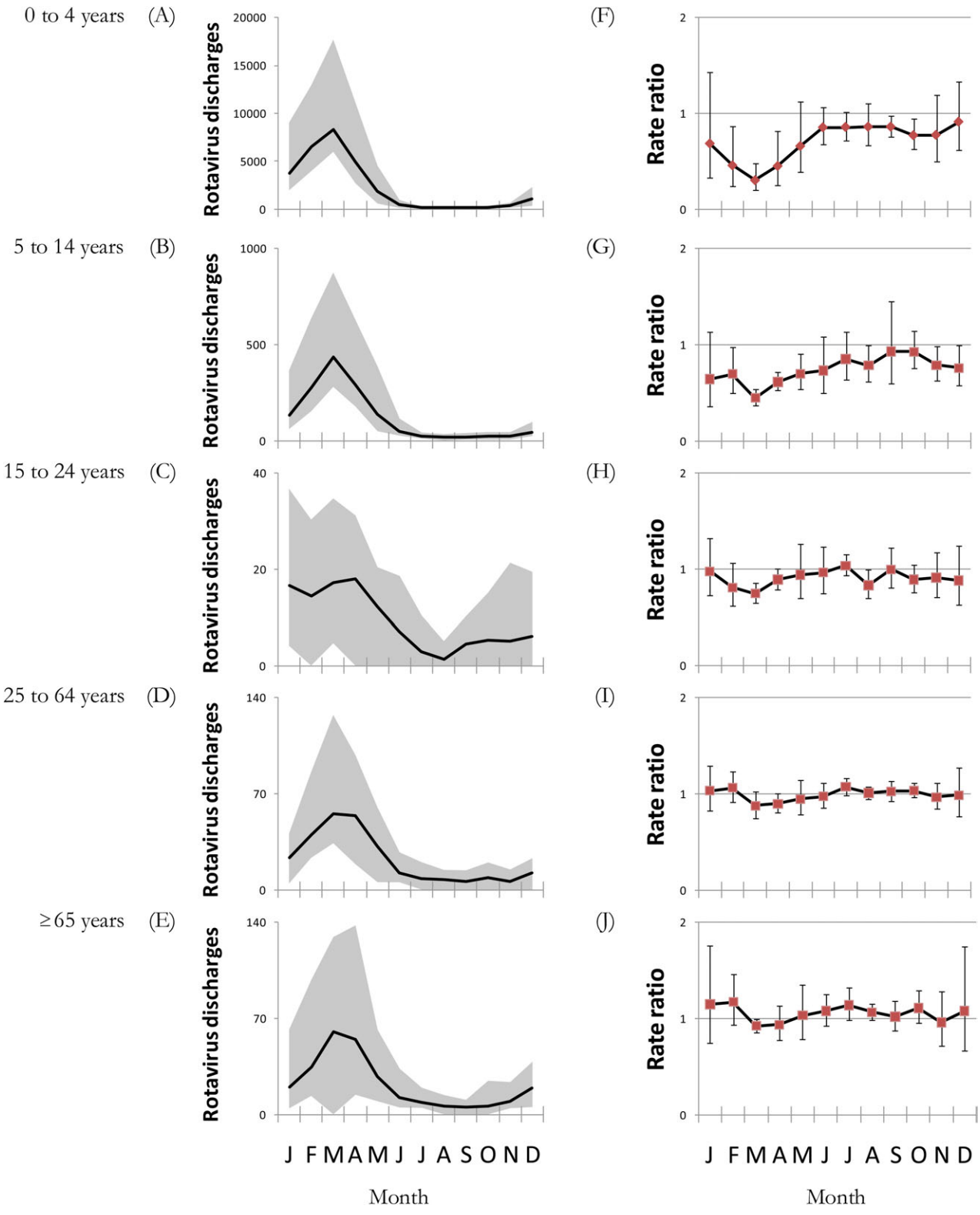

Figure 2. Monthly rotavirus hospitalizations in the prevaccine era (2000–2006), are shown in panels *A* to *E* with the monthly mean in black line and the range in shaded area. The age-specific monthly rate ratios of cause-unspecified hospitalizations in 2008 compared with the prevaccine era are shown in panels *F* to *J* (relative rate in red points; black bars represent the 95% confidence interval).

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Table 2. Rate Ratio of Rotavirus-Coded and Cause-Unspecified Gastroenteritis Discharges in 2008 Compared With the Prevaccine Era (2000–2006) by Sex, Race, and Region of the United States

Age group (y)	0–4, RR (95% CI)[a]	5–14, RR (95% CI)[a]	15–24, RR (95% CI)[a]	25–64, RR (95% CI)[a]	≥65, RR (95% CI)[a]
Rotavirus					
Sex					
Male	0.22 (.14–.34)	0.32 (.20–.51)	0.52 (.17–1.64)	0.72 (.37–1.42)	0.99 (.53–1.85)
Female	0.21 (.13–.33)	0.25 (.15–.41)	0.24 (.07–.84)	0.76 (.42–1.38)	0.69 (.40–1.19)
Race					
White	0.28 (.17–.45)	0.41 (.24–.71)	0.41 (.17–1.01)	0.68 (.36–1.29)	0.74 (.40–1.38)
Black	0.35 (.21–.59)	0.24 (.09–.64)	Insufficient data	0.72 (.18–2.83)	0.94 (.15–5.77)
Hispanic	0.19 (.10–.35)	0.16 (.07–.37)	0.21 (.03–1.58)	0.54 (.17–1.68)	0.23 (.04–1.28)
Other[b]	0.31 (.20–.49)	0.71 (.32–1.57)	Insufficient data	0.18 (.03–.98)	0.18 (.03–1.09)
Region					
Northeast	0.14 (.06–.31)	0.39 (.18–.83)	0.16 (.05–.52)	0.89 (.27–2.88)	0.70 (.24–2.02)
Midwest	0.16 (.10–.25)	0.15 (.07–.32)	0.45 (.08–2.6)	0.64 (.31–1.32)	0.56 (.26–1.23)
South	0.25 (.15–.43)	0.32 (.19–.55)	0.15 (.04–.60)	0.52 (.29–.92)	0.79 (.45–1.40)
West	0.28 (.17–.46)	0.31 (.16–.58)	2.82 (.63–12.6)	2.23 (.72–6.95)	2.86 (.79–10.29)
Cause-unspecified					
Sex					
Male	0.62 (.53–.72)	0.77 (.69–.86)	0.88 (.81–.96)	0.99 (.94–1.04)	1.04 (.95–1.13)
Female	0.61 (.52–.71)	0.68 (.61–.76)	0.96 (.89–1.03)	0.99 (.95–1.03)	1.02 (.96–1.09)
Race					
White	0.83 (.69–1.00)	0.96 (.85–1.08)	1.07 (.99–1.16)	1.17 (1.11–1.23)	1.18 (1.1–1.27)
Black	0.82 (.67–1.00)	0.85 (.69–1.04)	0.98 (.85–1.14)	0.97 (.9–1.05)	1.05 (.94–1.18)
Hispanic	0.45 (.37–.54)	0.58 (.49–.69)	0.83 (.71–.97)	0.83 (.76–.91)	0.80 (.72–.89)
Other[b]	0.86 (.71–1.05)	0.80 (.66–.97)	1.14 (.93–1.4)	1.06 (.96–1.17)	1.17 (1.05–1.31)
Region					
Northeast	0.50 (.39–.64)	0.67 (.56–.8)	0.86 (.78–.95)	0.96 (.9–1.03)	1.07 (.98–1.17)
Midwest	0.63 (.52–.76)	0.76 (.64–.9)	0.98 (.87–1.1)	1.00 (.94–1.07)	0.99 (.89–1.1)
South	0.73 (.62–.87)	0.74 (0.64–.86)	0.92 (.83–1.02)	1.00 (.95–1.06)	1.06 (.99–1.14)
West	0.49 (.4–.59)	0.65 (.56–.75)	0.92 (0.82–1.04)	0.99 (.93–1.05)	0.96 (.90–1.03)

[a] All models controlling for secular and seasonal variation.

[b] Asian or Pacific Islander, Native American, other.

vaccines have reduced efficacy in lower socioeconomic settings [20–24], but indirect protection via reduced household transmission may provide an important counterbalance to reduced efficacy in such settings.

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