Indirect Protection of Adults From Rotavirus by Pediatric Rotavirus Vaccination

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Background.   Pediatric vaccination has resulted in declines in disease in unvaccinated individuals through decreasing pathogen circulation in the community. About 2 years after implementation of pediatric rotavirus vaccination in the United States, dramatic declines in rotavirus disease were observed in both vaccinated and unvaccinated children. Whether this protection extends to adults is unknown.

Methods.   The prevalence of rotavirus, as determined by Rotaclone enzyme immunoassay, in adults who had stools submitted for bacterial stool culture (BSC) between February to May to Northwestern Memorial Hospital, Chicago, was compared between the prepediatric impact era (2006–2007) and the pediatric impact era (2008–2010). Isolates were genotyped and clinical characteristics of those with rotavirus were compared.

Results.   Of the 5788 BSC sent, 4725 met inclusion criteria and 3530 of these (74.7%) were saved for rotavirus testing. The prevalence of rotavirus among adults who had stool sent for BSC declined from 4.35% in 2006–2007 to 2.24% in 2008–2010 (a relative decline of 48.4%; $P = .0007$). The decline in the prevalence of rotavirus was of similar significant magnitude in both outpatients and inpatients. Marked year-to-year variability was observed in circulating rotavirus genotypes, with strain G2P[4] accounting for 24%; G1P[8], 22%; G3P[8], 11%; and G12P[6], 10% overall. About 30% of adults from whom rotavirus was isolated were immunocompromised and this remained constant.

Conclusions.   Pediatric rotavirus vaccination correlated with a relative decline of almost 50% in rotavirus identified from adult BSC during the peak rotavirus season, suggesting that pediatric rotavirus vaccination protects adults from rotavirus.

Keywords.   rotavirus; adult; pediatric; genotypes; indirect protection.

The prevention of disease in unvaccinated susceptible individuals due to vaccine-induced immunity in the population (eg, indirect protection) has been demonstrated in children with many different vaccines [1].

In addition, implementation of pediatric vaccines against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* resulted in significant declines of these pathogens in adults [2, 3].

Prior to the introduction of pediatric rotavirus vaccination, rotavirus was responsible for an estimated 24 million outpatient visits, 2.4 million hospitalizations, and 453 000 deaths in young children worldwide [4, 5]. Although almost all US children are infected at least once by age 5 [6], immunity from prior rotavirus infection is incomplete, partly due to different circulating genotypes, with subsequent infections occurring throughout life [7–9]. In 2008, 2 years after reintroduction of rotavirus vaccination in the United States, a dramatic decline was observed in rotavirus disease among both vaccinated and unvaccinated children,

suggesting indirect protection [10–14]. Studies in adults with diarrhea report the prevalence of rotavirus in the US to be approximately 3% to 18% [8, 9, 15, 16]; we have previously identified rotavirus in about 5% of adults requiring hospitalization who had stool sent for bacterial stool culture (BSC) between 1 February and 31 May 2006 [9]. The purpose of the current study was to investigate the impact of pediatric vaccination on adult prevalence, patient characteristics, and circulating rotavirus genotypes.

METHODS

This study was approved by the Northwestern University Institutional Review Board. Stools from adults (≥18 years) submitted for bacterial stool culture (BSC) to Northwestern Memorial Hospital ([NMH], Chicago, IL) were prospectively collected as a surrogate for clinically significant diarrhea [9, 17, 18]. All BSC samples were processed for routine bacterial stool pathogens (eg, *Salmonella*, *Shigella*, *Campylobacter*) but were not routinely tested for *Escherichia coli* O157:H7, Shiga toxin, or *Clostridium difficile*. Aliquots of remaining stool were frozen at −70°C for subsequent testing.

The primary outcome was to determine the prevalence of rotavirus in adults who had stools sent for BSC between the years immediately prior to the impact of pediatric rotavirus vaccination (2006–2007, the prepediatric impact era), and the years during which pediatric rotavirus vaccination resulted in a decline in pediatric disease (2008–2010, the pediatric impact era) [10–14]. Because we previously identified a marked winter-spring seasonality to adult rotavirus, with a peak occurring between February and May [9], we analyzed the prevalence of rotavirus in saved adult BSCs from 1 February to 31 May each year as determined by Rotaclone enzyme immunoassay (EIA; Meridian Bioscience Inc., Cincinnati, OH) [9, 19, 20]. The initial year, 2006, included only hospitalized adults, but was expanded in 2007–2010 to also include outpatients because data are lacking in this group. The 1 February through 31 May 2006 data have been previously published as part of a year-round epidemiological study of adult rotavirus [9].

We excluded formed BSCs, duplicates (BSCs submitted <7 days apart), BSCs from subjects <18 years of age, and BSCs from subjects who had been hospitalized >72 hours (to avoid including subjects with possible hospital-acquired diarrhea).

Secondary analyses included changes in the prevalence of disease among inpatients and outpatients who had BSCs sent. As in our prior study [9], subjects cared for in the emergency department (ED) for <18 hours were considered outpatients, while those cared for in the ED for ≥18 hours were considered inpatients. We also analyzed the change in prevalence of rotavirus per 10 000 hospital admissions among adults hospitalized at NMH between the 2 eras. We also compared the prevalence of routine bacterial stool pathogens in 2006–2007 with 2008–2010.

Reverse-Transcription Polymerase Chain Reaction Identification of the G and P Genotypes of Rotaclone-Positive Samples

Genetic identification of the G and P genotypes of Rotaclone EIA-positive samples was performed by RNA extraction followed by reverse-transcription polymerase chain reaction (RT-PCR) and gel electrophoresis using primer sets specific for G and P genotypes as previously described [9, 21]. Samples that had G and P genotypes identified were selectively confirmed by genetic sequencing and compared to known genotypes using the National Center for Biotechnology Information (National Institutes of Health, Bethesda, MD) Basic Local Alignment Search Tool. We also screened for the live attenuated rotavirus vaccine strains to determine if vaccine strains were responsible for symptomatic diarrhea in adults. In specimens in which a G-type or P-type could not be identified, we used nonspecific rotavirus primers followed by sequencing [21], as well as VP6 primers specific for RV5 (RotaTeq, Merck, Whitehouse Station, NJ) followed by sequencing, to determine if these sequences were similar to the bovine VP6 gene in RV5 [22]. We also sequenced the G1 genes of G1P[8] isolates to look for evidence of RV1 (Rotarix, GlaxoSmithKline, Brentford, UK).

Patient Characteristics

Demographic information, risk factors for acquisition, medical comorbidities, laboratory findings, and outcomes were abstracted from the medical records of those with rotavirus. Those who were HIV positive received >20 mg/day of prednisone-equivalent steroids for ≥2 weeks, had undergone stem cell or solid organ transplantation, or received chemotherapy or other immunomodulators (eg, methotrexate or monoclonal antibodies against tumor necrosis factor or a lymphocyte subset) were considered immunosuppressed [9]. Patient characteristics were compared between those from whom rotavirus was detected in 2006–2007 versus those from 2008–2010 to determine if changes occurred in this population over time.

Statistical Analysis

The prevalence of rotavirus was expressed as the number of subjects with Rotaclone-positive BSC divided by the total number of BSC available. We also repeated these calculations based on the total number of BSC collected to evaluate for a selection bias that might exist in those BSCs that were saved. Demographic and patient characteristics were summarized and compared between those who were Rotaclone positive from 2006–2007 and those from 2008–2010 using univariate analysis. Continuous variables that were normally distributed were tested using 2-sided t tests. Categorical variables were tested by either χ^2 or Fisher exact tests, depending on the distribution of the data. Some categorical variables were

reclassified as dichotomous in the event that a number of categorical classifications occurred with few or zero frequency counts. All analyses were performed using SAS Versions 9.2 and 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Change in Rotavirus Prevalence

Of the 5788 samples submitted for BSC during the months of February through May in 2006–2010, 1063 were excluded (Figure 1). Of the 4725 total eligible BSC samples, 3530 BSCs were saved (74.7%, interquartile range 64.1%–82.1% per month) for testing with Rotaclone EIA. The percentage of BSC that was saved for testing was higher in 2008–2010 (78.3%, 2541/3245) than in 2006–2007 (66.8%, 989/1480); $P < .0001$. Rotavirus was detected by EIA in 4.35% (43/989) of available BSC from 2006–2007; this declined to 2.24% (57/2541) during 2008–2010, a decline of 48.4% (an absolute decline of 2.11%; $P = .0007$, Figure 2). The prevalence of rotavirus among BSC was 2.15% in 2008, 2.67% in 2009, and 1.88% in 2010. The prevalence of rotavirus declined by 42.5% in hospitalized patients (5.91% to 3.40%; $P = .042$) and by 49.3% in outpatients (3.33% to 1.69%; $P = .016$). The decline in rotavirus-related hospitalizations at NMH between these 2 eras did not reach statistical significance (7.96/10 000 hospitalizations in 2006–2007 vs 5.89/10 000 hospitalizations in 2008–2010; $P = .28$).
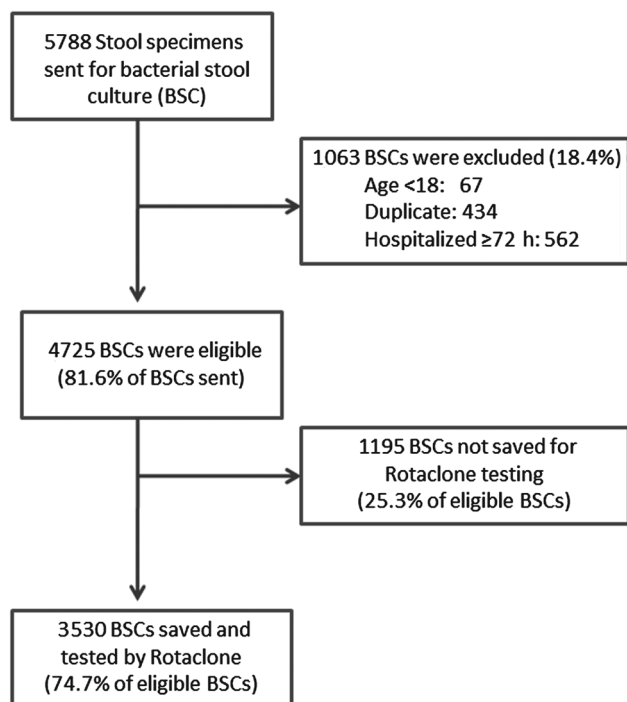
Stability of BSC Testing Over Time

We evaluated for evidence of change in behavior related to the sending and saving of BSCs between eras that could account for differences in the prevalence of rotavirus by comparing the prevalence of all bacterial pathogens routinely identified in BSC (eg, *Salmonella*, *Shigella*, *Campylobacter*) in the 2 eras. No change was observed in the percentage of hospital admissions in which a BSC was sent between 2006–2007 and 2008–2010 (2.57% vs 2.69%, respectively; $P = .31$). The combined prevalence of these common bacterial pathogens remained unchanged between 2006–2007 and 2008–2010 for both BSCs that were saved for rotavirus EIA testing (3.24% vs 3.66%, respectively; $P = .54$) and in all samples submitted for BSC (3.11% vs 3.39%, respectively; $P = .62$). In the prepediatric impact era (2006–2007), the prevalence of rotavirus (4.35%) was similar to the prevalence of all other bacterial pathogens routinely identified on BSC (eg, *Salmonella*, *Shigella*, *Campylobacter*) combined (3.24%; $P = .20$ for the difference in the prevalence). In contrast, the prevalence of rotavirus in the pediatric impact era (2008–2010, 2.24%) was lower than the combined prevalence of other routine bacterial pathogens (3.66%; $P = .0028$ for the difference). Because a selection bias could have occurred in BSCs that were saved, we also calculated the prevalence of rotavirus among the total number of eligible BSCs sent, and a similar 40% decline was noted (2.91% in 2006–2007 to 1.76% in 2008–2010; $P = .011$).

Rotavirus Genotypes

In 71% (71/100) of rotavirus-positive samples, both G- and P-types were identified. Over the 5 years of our study, G2P[4] accounted for 24%; G1P[8], 22%; G3P[8], 11%; and G12P[6],
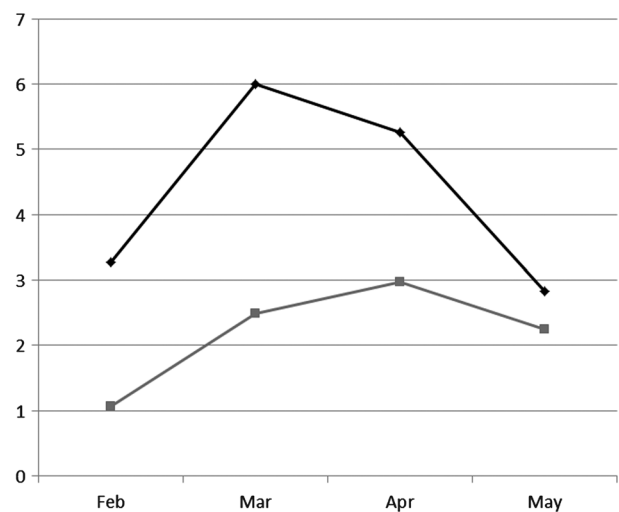

Figure 1. Study flow diagram.

Figure 2. Prevalence of rotavirus among stools sent for bacterial stool culture from adults; 2006–2007 (black), 2008–2010 (light gray). Full color version available online.
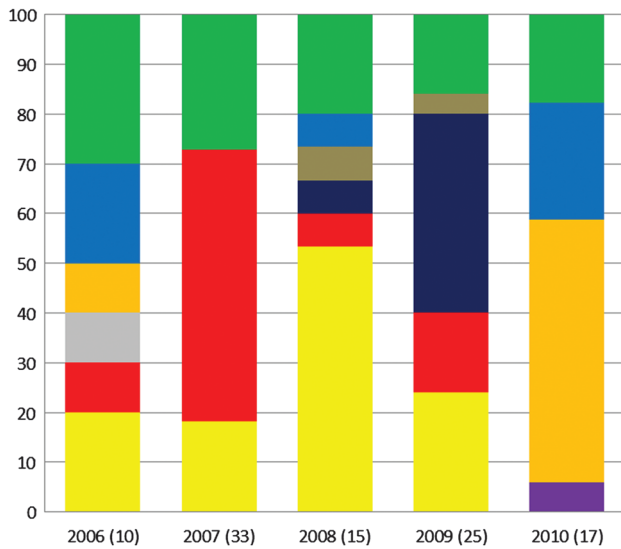
Figure 3. Rotavirus genotypes identified each year. The number of positive samples in a given year is in parentheses (n). Nontypeable (green); partially genotyped (light blue); G12P[6] (orange); G9P[4] (purple); G9P[8] (gray); G4P[8] (brown); G3P[8] (dark blue); G2P[4] (red); G1P[8] (yellow).

10% of isolates; although marked year-to-year variation in the predominant genotypes occurred (Figure 3). In 2006, no predominant rotavirus type circulated; in 2007, G2P[4] accounted for 55% of identified strains; in 2008, G1P[8] for 53%; in 2009, G3P[8] for 40%; and in 2010, G12P[6] accounted for 53% of the rotavirus types. Of the 7 isolates for which G- and P-typing was incomplete, G-nontypeable(nt)P[4] was identified in 3 isolates, GntP[6] in 2 isolates, GntP[9] in 1 isolate, and G12P[nt] in 1 isolate.

Among the 29 Rotaclone-positive isolates in which we were unable to completely genotype the rotavirus isolate, none of the amplified VP6 genes matched the vaccine RV5 backbone strain WC3. All of the 22 rotavirus isolates identified as G1P[8] had G1 sequences that matched wild-type G1P[8] better than RV1.

Coinfections

Coinfections in patients that were rotavirus positive were infrequently identified. Only 1/69 rotavirus-positive patients had *C. difficile* identified in the stool. No ova and parasites were identified among the 68 rotavirus-positive patients that had a microscopic examination performed. A single human immunodeficiency virus (HIV)–infected subject had a positive cryptosporidium EIA (ova and parasite microscopy was negative) and had already been responding to treatment for cryptosporidium with nitazoxanide before acute worsening of diarrhea symptoms occurred. In no rotavirus-positive sample was a routine bacterial pathogen identified (eg, *Salmonella*, *Shigella*, *Campylobacter*).

Demographics and Outcome

Demographic data and outcomes were similar for rotavirus-positive patients between 2006–2007 and 2008–2010 with several exceptions. Changes were noted in the ethnicity of those who were rotavirus EIA positive between the 2 eras ($P = .03$). The most pronounced changes occurred in those of Hispanic descent (increasing from 2.3% to 8.8%) and Asian descent (decreasing from 11.6% to 0%), although the numbers were small. The percentage of rotavirus-positive individuals with diabetes increased from 2.6% in 2006–2007 to 17.5% in 2008–2010 ($P = .022$). Notably, >30% of rotavirus-positive individuals were immunocompromised. Among those admitted, the mean duration of hospitalization was >2 days.

DISCUSSION

Our results showed that beginning in 2008, a 48.4% decline in adult rotavirus prevalence occurred from Feb to May compared to 2006–2007 ($P = .0007$). Notably, this decline was of similar magnitude in inpatients and outpatients. This decline in the prevalence of adult rotavirus beginning in 2008 directly corresponds to the declines of rotavirus observed in children [10–14]. Similar to reports in children, we observed less rotavirus in adults in 2008 and 2010 than in 2009 [12]. This is consistent with mathematical predictions of a shift toward a biennial peak in rotavirus disease [23]. We did not observe a statistically significant decline in rotavirus-related hospitalizations, probably due to the insufficient power of this study to detect such a difference. There is uncertainty about the longevity of the indirect protection in unvaccinated children; therefore, no prediction can be made about the sustainability of this decline [8, 12, 14, 24].

Because prior rotavirus vaccine cost-effectiveness calculations only took into account pediatric disease [25], an impact of pediatric vaccination on the burden of rotavirus in adults dramatically alters the cost effectiveness of pediatric vaccination. Data regarding the cost of rotavirus-related disease in adults are limited, but 1 US study estimated $152 million dollars in total rotavirus-related adult inpatient hospital charges each year [15]. Thus, although a 2.11% absolute decline of rotavirus prevalence in adults might appear small, a nearly 50% relative decline might translate to substantial healthcare savings because the decline was also observed among adult outpatients. Furthermore, because we observed declines in adult rotavirus disease that began in 2008 when only an estimated 32% of US children <5 years of age had received ≥1 dose of rotavirus vaccine [14], the ultimate decline in the prevalence due to childhood vaccination may be even greater.

Indirect protection of unvaccinated children has been observed [11, 12, 14]. Administrative data (eg, International Classification of Diseases [ICD]–based) from Australia and the United States have identified a decline in rotavirus-coded hospitalizations among children and young adults, suggesting indirect protection of unvaccinated individuals [13, 26]. Our experience is that rotavirus testing is very infrequently performed in adults, and that over 1 year the rotavirus-specific ICD code 008.61 was never used [17]. Thus, the failure of administrative data from Australia and the United States to find a decline in rotavirus-coded gastroenteritis among those >20–>24 years of age is not surprising [13, 26]. Our observation of the decline in rotavirus in adults extends evidence for the important indirect protection afforded by pediatric rotavirus vaccination.

We observed wide year-to-year variability in rotavirus genotypes, with the predominant circulating rotavirus genotype changing each year. Our genotype results are comparable to recently published US pediatric surveillance genotyping results from 2007–2009 [12, 27]. Notably, the marked predominance of G2P[4] in adult BSCs that we observed in 2007 was also observed in the study by Hull et al [27] in which G2P[4] accounted for >50% of the pediatric isolates observed in Chicago (the only year for which pediatric Chicago rotavirus data are available). The identification of G12P[6] in 2010 was not expected because this genotype has not been a commonly identified rotavirus genotype in US children, but has been increasingly observed in the United States and internationally [27–29]. Importantly, we did not identify either of the live attenuated rotavirus vaccines (RV5 or RV1) in any BSCs sent from adults. These data support prior arguments that the risk of wild-type rotavirus-related disease is much greater than the risk of live-attenuated vaccine-strain transmission and disease [6]. It is not known whether pediatric rotavirus vaccination will result in a genotype shift toward those genotypes not present in the vaccine (such as G12P[6]), similar to what has happened following other pediatric vaccination programs [2, 3].

The characteristics of adults from whom rotavirus was isolated remained similar between the 2 eras except for a change in ethnicity and the increased percentage of patients with diabetes. The clinical significance of these findings is uncertain. Similar to our prior data [9], about 30% of adults from whom rotavirus was isolated were immunocompromised. HIV was observed in about 10% of the cohort; however, no association was observed between CD4 lymphocyte cell count and the presence of rotavirus infection (data not shown).

Our study has some limitations. The study involved a single large urban US academic medical center and may not be generalizable. Confirmation of these data in other countries in which pediatric rotavirus vaccination has not been implemented will be important. We are unable to prove that pediatric vaccination caused the decline in the adult rotavirus, but this is a limitation of any study of indirect protection. Because rotavirus infections in children shifted to later in the season beginning in 2008 [11, 30], a shift outside the surveillance months would have been possible. Yet, data from the Centers for Disease Control and Prevention [30] suggest that the peak of rotavirus in Chicago children in 2008–2009 shifted only to April. Our data (Figure 2) also identified such a shift in the peak of adult rotavirus from March to April, but the peak clearly remained within the surveillance months. Our limited data from the prepediatric impact era might not identify a secular variation in prevalence. Because the pediatric burden of rotavirus disease in 2007 may have been impacted by vaccination, the year 2007 has been excluded from some pediatric rotavirus studies [11, 13, 14]. Thus, including the 2007 season may result in underestimating the impact. Although a change in physician ordering or the saving of BSC between 2007 and 2008 could account for the difference in rotavirus prevalence, our data suggests that this was unlikely. No change in the prevalence of bacterial pathogens was observed between the 2 eras, and the percentage of bacterial pathogens identified in this study was similar to prior studies [9, 18]. In addition, the percentage of inpatients from whom BSCs were sent remained stable over time (2.57% vs 2.69%; $P = .31$), arguing against an interval change in the sending of BSCs. In our prior study, which included the 2006 samples for which the lowest percentage of BSCs were available for additional testing, we found no difference between those that had a BSC sent and a BSC saved [9]. Thus, although it is possible that an unappreciated bias existed, we could not identify evidence supporting this. Our study was not powered to identify a decline in overall adult diarrhea morbidity or BSC testing, and the absolute decline in the prevalence of rotavirus does not allow such a calculation. Finally, coinfections were likely underestimated, particularly norovirus, because testing was not routinely performed [16].

In conclusion, our data document an almost 50% decline in the prevalence of rotavirus in adults during the peak rotavirus season. This decline began in 2008 and coincides with similar declines in children that were observed after widespread pediatric rotavirus vaccination. This observation strongly suggests that pediatric rotavirus vaccination protects adults from rotavirus. We observed marked year-to-year variation in the most prevalent rotavirus genotype in adults and observed the unusual genotype G12P[6] in 2010. Immunocompromised patients accounted for 30% of the rotavirus-positive population. Implementation of pediatric rotavirus vaccination should be encouraged for its substantial impact

on the prevalence of rotavirus in unvaccinated adults as well as in children.

Notes

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