CLINICAL AND VACCINE IMMUNOLOGY, Mar. 2009, p. 382–386 Vol. 16, No. 3
1556-6811/09/$08.00+0 doi:10.1128/CVI.00382-08

Decline in Cases of Rotavirus Gastroenteritis Presenting to The Children's Hospital of Philadelphia after Introduction of a Pentavalent Rotavirus Vaccine▽

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Received 21 October 2008/Returned for modification 18 November 2008/Accepted 12 January 2009

A pentavalent rotavirus vaccine for infants became available in the United States in February 2006. By 2007, vaccination rates nationwide were estimated to be ~50%. We studied the effectiveness of the vaccine in a real-world setting outside of a clinical trial. All children presenting to The Children's Hospital of Philadelphia with acute gastroenteritis have been monitored for the presence of rotavirus antigen in the stool by enzyme-linked immunosorbent assay (ELISA [followed by genotyping if ELISA positive]) since the 1994-1995 epidemic season, presenting a unique opportunity to assess the impact of the recently introduced vaccine. The annual number of community-acquired cases over the preceding 13 years had approached or exceeded 100, with 271 cases in 2005 to 2006 and 167 cases in 2006 to 2007. In the 2007-2008 season, only 36 community-acquired cases were identified, representing an 87% reduction from the same period in 2005 to 2006. G3 was the predominant serotype, accounting for 15 community cases (42%). Our study is limited by its observational design using historical comparisons. Nonetheless, the abrupt decline in rotavirus gastroenteritis cases during the 2007-2008 season likely resulted from vaccination. Because protection rates appeared to have exceeded vaccination rates, herd immunity may have contributed to some degree to the effectiveness of the vaccine.

Rotavirus is the leading cause of dehydrating acute gastroenteritis in infants and young children around the world and continues to infect virtually all infants and children by the age of 5 years, the great majority in the first 2 years of life (14). Rotavirus infections account for approximately a half-million deaths annually in the developing world. In the United States, where ~50 deaths attributable to rotavirus are reported each year, rotavirus infections cause an estimated 50,000 to 70,000 hospitalizations per year.

The rotavirus epidemic season in the United States typically begins in the late autumn in the Southwest and then appears sequentially in other regions extending in a northeasterly direction until peaking in New England in mid-spring. In Philadelphia, rotavirus cases are usually seen first in January and the number of cases typically peaks by March or April, after which cases decrease rapidly until virtually disappearing by the end of June (4). Multiple rotavirus serotypes usually circulate during a local epidemic. Overall, G1P1A[8] is the most common serotype causing human disease throughout the world, but outbreaks in which G3, G9, or G2 rotaviruses were atypically prominent have been seen in Philadelphia during the last 14 years (4).

Two new rotavirus vaccines have recently been licensed in the United States: a pentavalent human-bovine reassortant vaccine (5, 17) expressing human serotypes G1, G2, G3, G4, and P1A[8] (RotaTeq; Merck, Whitehouse Station, NJ), licensed in February 2006, and an attenuated human rotavirus vaccine (16) composed exclusively of a single G1P1A[8] strain (Rotarix; GlaxoSmithKline, London, England), licensed in April 2008. Both vaccines were highly efficacious in large phase III clinical trials (16, 17). The longstanding surveillance system for acute gastroenteritis at The Children's Hospital of Philadelphia (CHOP) provided a unique opportunity to assess the impact of the pentavalent vaccine in actual clinical practice.

MATERIALS AND METHODS

The protocol was approved by the institutional review board at CHOP. Referral patterns have been previously described (6). Informed consent from legal guardians was not required to procure and process stool specimens already obtained from children with acute gastroenteritis as part of standard clinical practice. If a bulk sample was not available, rectal swabs were only accepted if fecal staining was visible. Based on prior experience, the rotavirus epidemic season in Philadelphia was defined as the 7-month period from 1 December through 30 June of the following year (4). For 14 consecutive rotavirus seasons (from 1994 to 1995 through 2007 to 2008), all children presenting to CHOP with gastroenteritis and having evaluable stool samples were tested by a commercial qualitative enzyme-linked immunosorbent assay (ELISA) for rotavirus antigen (Premier Rotaclone; Meridian Bioscience, Cincinnati, OH). Beginning with the 1999-2000 season, ELISA-positive specimens were submitted to Merck Research Laboratories for genotyping by reverse transcriptase PCR if the quantity of the stool sample permitted (9).

RESULTS

Ongoing surveillance at CHOP has shown steadily increasing numbers of rotavirus ELISA-positive cases of community-

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▽ Published ahead of print on 21 January 2009.

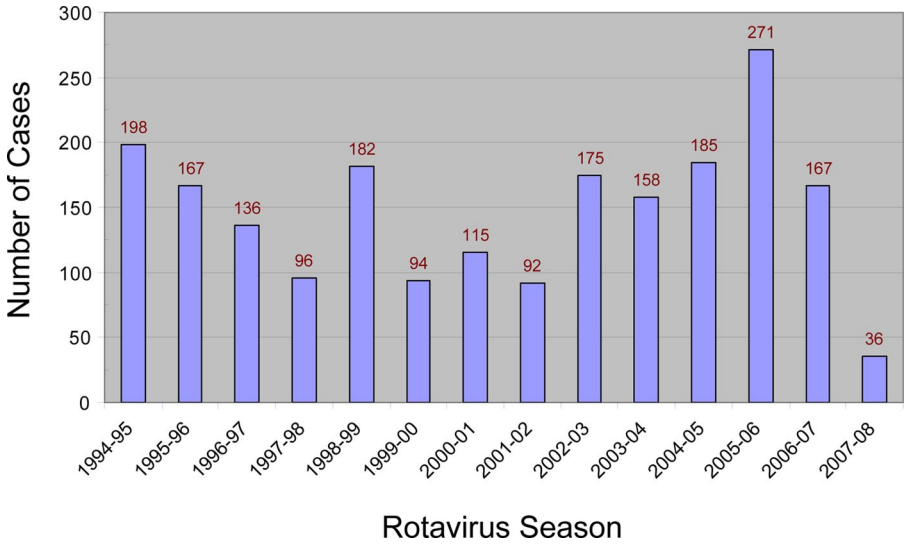

FIG. 1. Number of community-acquired rotavirus cases presenting to CHOP for the last 14 rotavirus epidemic seasons (1994 to 2005 through 2007 to 2008). On the basis of historical experience, the rotavirus epidemic season in Philadelphia was considered to extend from December through the following June. The collection of samples was incomplete during the 2002-2003 rotavirus season, when only 29 of 175 ELISA-positive specimens were available for serotyping. During the 2007-2008 season, 36 community-acquired cases were seen at CHOP. For the preceding 13 seasons, the mean number of cases was 157 (95% confidence interval, 126 to 187) and the median number of cases was 167 (interquartile range, 106 to 184).

acquired gastroenteritis from the 1994-1995 season until the 2005-2006 season (Fig. 1). The highest number of community-acquired cases ($n = 271$) was observed in 2005 to 2006. In 2006 to 2007 (the first full rotavirus season following approval of the pentavalent vaccine by the U.S. Food and Drug Administration), the number of cases declined to 167. In the 2007-2008 season, 36 community cases were identified compared to a mean of 157 (95% confidence interval, 126 to 187) cases over the preceding 13 seasons. The number of cases in 2007 to 2008 represented an 87% reduction compared to the same period in 2005 to 2006 (the last rotavirus season before the pentavalent vaccine became widely available). In contrast, the frequency and pattern of winter-spring respiratory viruses in the CHOP population were essentially stable from the 2005-2006 through 2007-2008 seasons. For example, there were 1,449 positive tests for respiratory syncytial virus for 2007 to 2008, compared to 1,367 for 2005 to 2006; the corresponding numbers for influenza A virus were 336 versus 354. Twelve (33%) of the patients presenting with rotavirus gastroenteritis in 2007 to 2008 were presumably not vaccinated because they were already >32 weeks old before the vaccine became available (1). In addition, four children ≤2 months of age should have received at most the first dose of vaccine based on current recommendations. Of the five patients (ages 2, 8, 11, 16, and 21 months at the time of their rotavirus gastroenteritis) for whom immunization histories were accessible, the 8-month-old child and 11-month-old child had each received a single dose of rotavirus vaccine and the other three children had not been vaccinated. Overall, 32 (89%) patients were kept overnight in the emergency department holding area ($n = 3$) or admitted to the hospital ($n = 29$) for a median duration of 2 days.

In 2007 to 2008, rotavirus cases appeared later than in previous years (Fig. 2). The peak number of cases occurred in May for the 2007-2008 season and in April for the 2006-2007 season; only once during the prior 12 seasons had the most cases been seen in April, usually peaking in March ($n = 7$) or earlier. Despite year-round testing, no cases of rotavirus gastroenteritis were identified at CHOP from July 2008 through November 2008.

Proportionately more cases were seen in children >18 months of age in 2007 to 2008 than in historical controls (Fig. 3). The median age of patients seen in 2007 to 2008 increased to 20 months from 11 months (range, 8 to 14 months) over the preceding 13 seasons. However, the absolute number of cases in children ≥3 years of age decreased from 42 (15%) in 2005 to 2006 to 10 (28%) in 2007 to 2008, even though these patients were too old to have received the vaccine according to published recommendations (8).

VP7 genotyping of the 36 community isolates in 2007 to 2008 revealed 11 G1, 3 G2, 15 G3, 1 G4, 1 G9, 1 G12, and 4 nontypeable cases (Fig. 4 and Table 1). There were no cases caused by the bovine G6 strain used in the pentavalent vaccine during the 2007-2008 season, but one bovine G6 case was identified in 2006 to 2007. Although G3 rotaviruses had not caused a substantial fraction of cases at CHOP since the 1994-1995 season, G3 was the predominant serotype among the 2007-2008 rotavirus cases, accounting for 42% of the community-acquired infections. All of the VP4-typeable cases were P1A[8], except for one case each of G1P1B[4] and G2P1B[4]. Of the two G2 cases with identifiable VP4 types, one was associated with the typical P1B[4], whereas the other was associated with P1A[8], which has only uncommonly been linked to G2 strains. The absolute number of nosocomial cases in 2007 to 2008 was unchanged from 2005 to 2006 but represented a larger fraction of the cases as a result of the decline in community-acquired cases. VP7 typing of the 14 nosocomial cases in 2007 to 2008 revealed 1 G1, 3 G2, 7 G3, and 3 nontypeable cases. All serotypes causing nosocomial infections

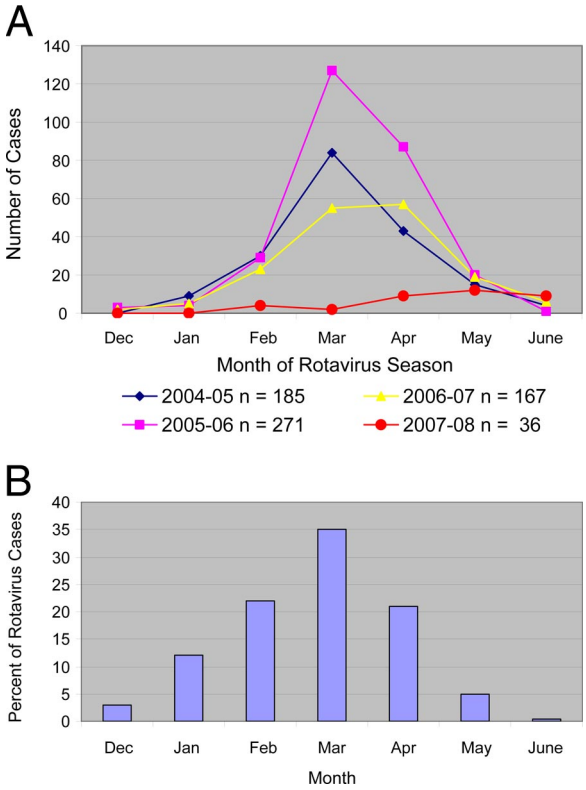

FIG. 2. (A) Number of community-acquired rotavirus cases presenting to CHOP for the last four rotavirus epidemic seasons (from 2004 to 2005 through 2007 to 2008) by month. The total number of ELISA-confirmed rotavirus cases during the 2007-2008 season was 50, including 36 community-acquired and 14 nosocomial cases. Table 1 gives the VP7 serotypes of the community-acquired cases of rotavirus gastroenteritis presenting to CHOP over the last four epidemic seasons. (B) Seasonality of the rotavirus epidemic season prior to licensure of the pentavalent rotavirus vaccine. The overall percentage of ELISA-confirmed community-acquired cases of rotavirus gastroenteritis presenting to CHOP is shown by month for the combined seasons from 1994 to 1995 through 2005 to 2006. The peak annual incidence was generally seen in March.

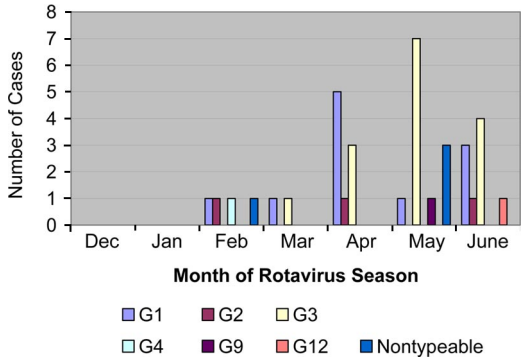

FIG. 4. Serotype distribution of community-acquired rotavirus cases presenting to CHOP during the 2007-2008 epidemic season. Genotyping of the 36 community isolates in 2007 to 2008 revealed 10 cases of G1P1A[8]; 14 cases of G3P1A[8]; 3 cases of (G-nontypeable)P1A[8]; and 1 case each of G1P1B[4], G2P1A[8], G2P1B[4], G2/QNS (QNS, quantity not sufficient), G3(P-nontypeable), G4P1A[8], G9P1A[8], G12P1A[8], and nontypeable. Genotyping of the 14 nosocomial cases in 2007 to 2008 revealed 2 cases of G2P1B[4]; 7 cases of G3P1A[8]; 2 cases of (G-nontypeable)P1A[8]; and 1 case each of G1P1A[8], G2(P-nontypeable), and nontypeable. All serotypes causing nosocomial infections appeared earlier in the community.

had previously been identified among the community-acquired cases.

DISCUSSION

A pentavalent rotavirus vaccine was licensed in the United States in February 2006 and recommended later in the same month for universal use by the Advisory Committee on Immunization Practices as a three-dose series to be given at 2, 4, and 6 months of age (1). The formal recommendation for use of the pentavalent rotavirus vaccine warns not to administer any dose of the vaccine to children >32 weeks old because of a possible age-related risk of intussusception. By the summer of 2007, the Centers for Disease Control and Prevention reported that vaccination rates had approached 50% in five sentinel cities (2, 3). A public health official in Philadelphia unofficially estimated that the overall coverage rate in the city as of mid-2008 was near 60%, but uptake of the vaccine may vary by

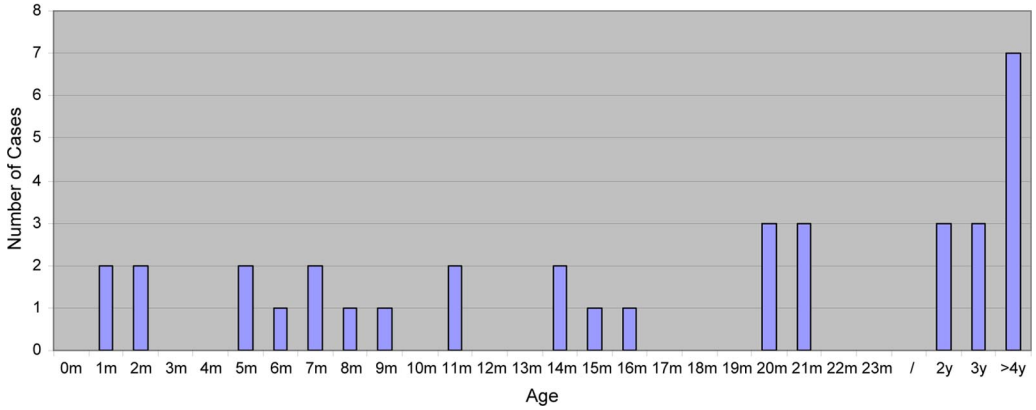

FIG. 3. Age distribution of community-acquired rotavirus cases presenting to CHOP during the 2007-2008 epidemic season. m, months; y, years. For 13 years prior to the 2007-2008 season, the median age of children seen at CHOP with rotavirus gastroenteritis ranged from 8 to 14 months. The median age of cases during the 2007-2008 season was 20 months.

TABLE 1. VP7 serotypes of the community-acquired cases of rotavirus gastroenteritis presenting to CHOP over the last four epidemic seasons

Rotavirus season	No. of cases with serotype:							
	G1	G2	G3	G4	G8	G9	G12	Total[a]
2004–2005	161	9	3	0	0	2	10	185
2005–2006	134	101	4	0	1	21	0	261
2006–2007[b]	153	3	7	0	0	0	1	164
2007–2008	11	3	15	1	0	1	1	32

[a] Only includes VP7-typeable strains.
[b] One isolate was a bovine G6 (consistent with reassortant rotavirus used in the pentavalent vaccine).

neighborhood and practice (7). All children presenting to CHOP with acute gastroenteritis have been monitored for the presence of rotavirus antigen in the stool since the 1994-1995 epidemic season, presenting a unique opportunity to assess the impact of the availability of the pentavalent rotavirus vaccine. We studied the effectiveness of the vaccine in a real-world setting outside of a clinical trial.

The abrupt and dramatic decline in rotavirus gastroenteritis cases between the 2005-2006 and 2007-2008 seasons was likely attributable to increasing uptake of the recently introduced vaccine (2). The theoretical possibility that vaccinated children who subsequently developed symptomatic rotavirus gastroenteritis severe enough to result in a hospital visit might have had falsely negative rotavirus ELISA results due to limited viral replication in the gut seems biologically implausible. Unfortunately, we did not have complete access to the vaccination histories of individual children presenting to CHOP with rotavirus gastroenteritis during the 2007-2008 season, but a third of patients should not have been given a dose of the rotavirus vaccine based on the upper-age restriction; another 11% were too young to have received any more than one dose, if vaccinated at all (8, 10). None of the five children with rotavirus gastroenteritis whose immunization status could be ascertained had received more than a single dose of the three-dose vaccine series.

Because protection rates appear to have exceeded vaccination rates, some degree of herd immunity (with or without a minor element of contact immunization as the result of shedding by vaccinated children) may have further contributed to the overall effectiveness of the vaccine. Except for a single case over the last 2 years, vaccine strains have not been demonstrated in children with rotavirus gastroenteritis severe enough to be brought to CHOP. A decrease in the number of susceptible children could explain the late appearance of rotavirus cases in 2007 to 2008, observed not only in Philadelphia but throughout the United States (2, 13). Herd immunity might also be responsible for the absolute reduction of cases in children who were too old to have been vaccinated.

Although G1 has usually been the most common serotype identified in children presenting to the hospital with rotavirus gastroenteritis (4), G3 rotaviruses predominated during the 2007-2008 season in the Philadelphia area served by CHOP, causing 15 (47%) of the 32 VP7-typeable community cases. Despite G3 and P1A[8] both being contained in the pentavalent vaccine, the widespread use of the vaccine could have led to the apparent emergence of G3 strains in 2007 to 2008 as well as the associated decline in overall case frequency. Alternatively, the serendipitous appearance of a less contagious and/or less virulent G3 strain independent of the introduction of the vaccine may be responsible for the decline in rotavirus cases presenting to the hospital. However, in the 1994-1995 season (predating the short-lived availability of the tetravalent rhesus-human reassortant rotavirus vaccine [RotaShield; Wyeth, Madison, NJ] during 1998 to 1999), when G3 rotaviruses last played a major role in the Philadelphia epidemic (93% of the typed cases), the timing and total number of community-acquired cases ($n = 198$) resembled patterns from other years (2). Continuing surveillance will test whether these trends are chance variation or sustained by expanding vaccine coverage.

Our study is subject to all the limitations of an observational study using historical controls. Unrecognized covariates other than vaccination (such as decreased virulence of circulating rotavirus strains or changing referral patterns at our hospital) and random variation may have been responsible for the results. However, the quantitatively similar observations concurrently reported from another hospital in a different neighborhood of Philadelphia (8) as well as from several other sites across the United States (10–12, 15) support our tentative conclusion that vaccination is the most likely and parsimonious explanation for the declining incidence of rotavirus gastroenteritis at our institution.

ACKNOWLEDGMENTS

We thank Darcy Hille, Max Ciarlet, Karyn Davis, Sheila Nolan, and Joann DiLullo for advice and support.

This study was funded in part by Merck & Co., Inc., which markets the pentavalent rotavirus vaccine under the brand name RotaTeq. The paper underwent formal review by the sponsor. HF.C. is the coinventor of the pentavalent rotavirus vaccine and is an investigator and consultant for Merck. L.M. and M.J.D. are employees of Merck Research Laboratories and may own stock and/or stock options in the company.

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