Evaluation of Rotavirus Vaccine Effectiveness in a Pediatric Group Practice

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Vaccines are traditionally tested under the optimal conditions of clinical trials (efficacy). However, their public health impact is better assessed under the real conditions of a clinical practice (effectiveness). The authors aimed to estimate the effectiveness of a rotavirus vaccine (rhesus rotavirus vaccine-tetravalent (RRV-TV)) to prevent rotavirus-related hospitalization among children ≤3 years of age. They reviewed computer records from an urban pediatric practice in New Orleans, Louisiana, comprising 1,413 children born between April 1, 1998, and June 1, 1999, and who would have been eligible to receive RRV-TV. They also reviewed hospital records to determine rotavirus hospitalizations for gastroenteritis during October 1998–June 2001. A total of 1,099 children were enrolled, 513 unvaccinated and 586 vaccinated. The attack rate of rotavirus hospitalization was 0.34 per 100 child-years—0.52 for unvaccinated (no doses) children, 0.20 for partially vaccinated (one or two doses) children, and 0 for fully vaccinated (three doses) children. Protective vaccine effectiveness was 70% (95% confidence interval (CI): –43, 94) among vaccinated children, 61% (95% CI: –86, 92) among partially vaccinated children, and 100% (95% CI: –120, 100) among fully vaccinated children. One episode of rotavirus-associated hospitalization was prevented per 104 infants partially vaccinated and per 64 infants fully vaccinated.

child; public health; rotavirus; vaccination

Abbreviations: CI, confidence interval; RRV-TV, rhesus rotavirus vaccine-tetravalent.

Rotavirus infection is the main cause of severe, dehydrating diarrhea in infants and young children, leading to significant morbidity and mortality worldwide. In the United States, rotavirus causes more than 3 million cases of diarrhea, 50,000 hospitalizations, and 20–40 deaths annually (1, 2). Seventy-two percent of rotavirus hospitalizations occur by age 2 years and 90 percent by age 3 years (3–5). The burden and cost associated with the disease led to development of specific vaccines (6). The rhesus rotavirus vaccine-tetravalent (RRV-TV) (Rotashield; Wyeth Laboratories, Inc., Marietta, Pennsylvania) provided 80 percent protection (95 percent confidence interval (CI): 56, 91) against severe rotavirus illness in prelicensure studies (7) and in October 1998 became the first licensed rotavirus vaccine. In Louisiana, RRV-TV was made widely available soon after licensure, and the vaccine was recommended but not made mandatory by the state; Medicaid and other insurers provided reimbursement. Unfortunately, postlicensure surveillance unveiled an infrequent (1:5,000–10,000 vaccinated infants), but definitive association between RRV-TV administration and the occurrence of intussusception 1–2 weeks following vaccination (8, 9). As a result, RRV-TV was withdrawn from the market in July 1999, after less than 1 year of use (10, 11).

Prelicensure studies normally evaluate the protection conferred by a vaccine under the optimal conditions of clinical trials (i.e., vaccine efficacy). These trials give a good estimate of the potential value of a vaccine. However, from the patient and public health perspective, the real utility of a vaccine is better estimated by its performance when applied...
rotavirus-associated hospitalization among children. Efficacy figures from vaccine trials cannot easily be converted to vaccine effectiveness because, during routine practice, not all susceptible children will be immunized before exposure or receive a full vaccination series, which will diminish the effectiveness of vaccination programs. In addition, the spectrum of vaccine recipients in practice typically expands beyond the healthy, highly responsive groups usually selected for efficacy trials (12, 13). Vaccines that prove safe and protective in efficacy trials should then have their effectiveness determined, which requires evaluating the impact of vaccination on practical outcomes of public health importance, analyzed from the onset of vaccination in all targeted persons who might realistically receive the vaccine in routine practice settings. RRV-TV demonstrated good efficacy in several prelicensure trials, particularly in preventing severe rotavirus gastroenteritis (14–19), but information is limited about its effectiveness.

The aim of this study was to estimate the effectiveness of rotavirus immunization in a pediatric practice to prevent rotavirus-associated hospitalization among children ≤3 years of age during three rotavirus seasons (1998–1999, 1999–2000, and 2000–2001) compared with the efficacy reported in the literature (7).

MATERIALS AND METHODS

Study population

Study participants included children born between April 1, 1998, and June 1, 1999, who receive primary medical care at a large urban pediatric practice in New Orleans, Louisiana. Primary care providers from this practice admit their patients to Children’s Hospital of New Orleans, the largest pediatric hospital in Louisiana. The birth period was chosen to include children who would have been eligible to receive RRV-TV when the vaccine was available (October 1998–July 1999). Children who had immunosuppressive disorders and children with allergies to a vaccine component for whom rotavirus vaccination was contraindicated were excluded from the study. The study was approved by the Institutional Review Board of Louisiana State University Health Sciences Center in New Orleans.

Databases

Two databases provided the information on patients and encounters. The first is a computerized list at the pediatric practice that includes patients’ identifiers (name, record number, date of birth, gender, and home residence zip code), insurance type, immunization registry, and billing codes with descriptors for all outpatient encounters (health-supervision and sick visits). The second is a computerized list at Children’s Hospital of New Orleans containing inpatient (hospitalization) and outpatient (emergency department) records with information on patients’ identifiers, date of admission, admitting and referring physicians, and admission and discharge diagnoses.

Baseline data

The pediatric practice records were reviewed to identify potential subjects to be enrolled. To participate in the study, a child had to meet the following three criteria.

Eligibility. Required was birth between April 1, 1998, and June 1, 1999, and lack of diagnostic International Classification of Diseases, Ninth Revision, Clinical Modification codes corresponding to immunosuppressive or other conditions that would have contraindicated administration of RRV-TV (20). Children of either gender and of any race or ethnicity group were potential candidates.

Availability. To determine that the child had been under the practice’s care at the age when he or she would have been eligible to receive RRV-TV (approximately at 2, 4, and 6 months of age), billing codes were reviewed to verify administration of diphtheria-tetanus-pertussis vaccine.

Follow-up. Billing codes were reviewed to verify administration of measles-mumps-rubella vaccine (at 12—15 months of age) as an indicator that the subject was under the practice’s care for at least 1 year.

Baseline information was obtained on subjects enrolled, including number of doses of RRV-TV administered, date of birth, gender, insurance type, and home residence zip code (converted into estimated household income by using 1990 US census data (21)). Subjects who received no doses of RRV-TV were considered unvaccinated, and subjects who received at least one dose were considered vaccinated. The latter group was divided into partially vaccinated (one or two doses) and fully vaccinated (three doses). Each child contributed a period equivalent to the time between being 10 weeks of age (2 weeks after becoming eligible for the first RRV-TV dose) and either until age 15 months (upper range for measles-mumps-rubella vaccination), the documented date on which the child was seen last (after 15 months of age), development of the outcome of interest (rotavirus hospitalization), or the end of the observation period (June 30, 2001).

Outcome data

Records corresponding to three rotavirus seasons (October 1998–June 1999, July 1999–June 2000, and July 2000–June 2001) were reviewed for the occurrence of the following three events.

Acute gastroenteritis. The pediatric practice and Children’s Hospital of New Orleans databases were reviewed to determine the occurrence of office visits, emergency department visits, and hospitalizations associated with gastroenteritis for each participating subject, as indicated by International Classification of Diseases, Ninth Revision, Clinical Modification codes 008.6 (008.61), 008.8, and 009.0–009.3. For each case identified, the medical record was reviewed to determine the appropriateness of the gastroenteritis diagnosis. Acute gastroenteritis was defined as vomiting (forceful expulsion of gastric contents), diarrhea (three or more looser-than-normal stools during a 24-hour period), or both (7). Records were reviewed blinded to the vaccination status of the subjects.

Rotavirus hospitalization. For each hospitalized case, laboratory information was reviewed to determine whether...
the subject was tested for rotavirus infection and the test result. Rotavirus gastroenteritis was defined as a case of acute gastroenteritis with detection of rotavirus antigen in stool using an enzyme immunoassay.

Serious adverse events. The number of cases of intussusception (International Classification of Diseases, Ninth Revision, Clinical Modification code 560.0) in each study group was recorded, as well as the number of deaths due to severe rotavirus illness.

Data analysis

To determine vaccine protection, we considered only rotavirus hospitalizations that began at least 2 weeks after the child was eligible for the first dose of RRV-TV. Vaccine protection was calculated as protective efficacy (PE) and was determined by using the following formula (13): PE = [(ARU – ARV)/ARU] × 100, where ARU is the attack rate of rotavirus gastroenteritis hospitalization in unvaccinated subjects and ARV is the attack rate in vaccinated subjects. This index measures the proportionate reduction in the disease outcome associated with vaccination, reflecting performance of the vaccine independent of the level of incidence of disease in unvaccinated subjects. A second index of vaccine protection is the rate difference, determined by using the following formula: ARU – ARV. The reciprocal of the rate difference measures the number of rotavirus hospitalizations that would be prevented per 1,000 infants vaccinated (12, 13). Confidence intervals were calculated at the 95 percent level, as recommended previously (13); for rates approaching 0, confidence interval calculations were based on the relation between the F test distribution and the binomial distribution. Categorical variables were subjected to chi-square analysis or Fisher’s exact test where applicable by using SPSS software (version 10.1 for Windows; SPSS Inc., Chicago, Illinois).

RESULTS

Study population

The pediatric practice database contained information on 1,413 children born between April 1, 1998, and June 1, 1999. A total of 314 children (22 percent) were excluded from the study because they did not fulfill the availability and/or follow-up criteria for enrollment. Excluded children were similar to the enrolled ones in terms of gender distribution, month of birth, and estimated household income but were significantly different (p < 0.001) regarding their insurance coverage; that is, they were more likely to have Medicaid or no insurance and less likely to be enrolled in a health maintenance organization (HMO).

Of the 1,099 children enrolled, 513 (47 percent) were unvaccinated (no doses) and 586 (53 percent) were vaccinated (one or more doses). The latter group included 438 partially vaccinated (n = 200, one dose; n = 238, two doses) and 148 fully vaccinated (three doses) children. Both groups (unvaccinated, vaccinated) were comparable with regard to gender distribution, medical insurance coverage, and estimated household income (table 1). The month-of-birth distribution differed between the two groups, with the unvaccinated subjects corresponding to earlier cohorts (figure 1). Furthermore, utilization of the pediatric practice differed; vaccinated children had more office visits than unvaccinated ones (median: 14 vs. 12, respectively). Among vaccinated children, the median ages at which the first, second, and third doses of RRV-TV were administered were 10, 19, and 26 weeks, respectively, and the median ages at which vaccination was started was similar for the three subgroups: 9 weeks (range: 7, 30), 12 weeks (range: 7, 29), and 8 weeks (range: 7, 28) for the one-, two-, and three-dose subgroups, respectively. The partially vaccinated children (one or two doses) were significantly younger than those fully vaccinated (three doses) (p < 0.001), with 53 percent of the former born during the last 6 months of the observation period.

Acute gastroenteritis

Over the 3-year period, 285 episodes of gastroenteritis requiring medical attention were detected among vaccinated children (rate: 0.22 per child-year); 246 children were seen in the pediatric office, 35 were seen in the emergency department, and four were hospitalized. Among the unvaccinated children, 332 episodes of gastroenteritis (rate: 0.24 per child-year) occurred; 277 children were seen in the office, 44 were seen in the emergency department, and 11 were hospitalized. The various rates were not significantly different between the two groups (vaccinated, unvaccinated).

Rotavirus hospitalization

Fifteen children were hospitalized for acute gastroenteritis during the observation period, an overall attack rate of 0.56 per 100 child-years. The median age at the time of hospitalization was 10 months (range: 3, 28), and the average length of stay was 2 days (range: 1, 4). Of the 15 children hospitalized, 11 underwent stool testing for rotavirus and nine of...
them had confirmed rotavirus gastroenteritis (0.34 per 100 child-years). Of these, seven were unvaccinated and two were vaccinated (two doses of RRV-TV each). Seasonality was evident among children with confirmed rotavirus hospitalization, with peak activity occurring between December and April (figure 2). All four children not tested for rotavirus were unvaccinated. The reason for lack of rotavirus testing in these cases was not obvious from reviewing the records, but likely explanations include presentation of two cases during months of low rotavirus circulation in the community (August 1998 and August 1999) and no bowel movement in two cases during hospitalization.

Vaccine efficacy

Table 2 shows the attack rates of rotavirus-associated hospitalization according to vaccination status. The overall attack rates for the entire observation period were 0.52 and 0.15 per 100 child-years for unvaccinated and vaccinated children, respectively, for an estimated efficacy of 70 percent. Since no fully immunized subject was hospitalized with rotavirus, the protective efficacy of the vaccine for this subgroup was 100 percent, and it was 61 percent for partially immunized children. On the basis of the observed attack rates, one episode of rotavirus gastroenteritis requiring hospitalization was prevented for every 90 vaccinated, 104 partially vaccinated, and 64 fully vaccinated children. Stratified analyses produced similar vaccine efficacy estimates for the two income categories ($\leq$22,000, 70 percent (95 percent CI: –171, 97) and >$22,000, 69 percent (95 percent CI: –194, 97) and the two age cohorts (date of birth April 1998–October 1998, 58 percent (95 percent CI: –255, 95) and date of birth November 1998–June 1999, 75 percent (95 percent CI: –179, 98)). The adjusted overall vaccine efficacy esti-

<table>
<thead>
<tr>
<th>TABLE 1. Sociodemographic characteristics of children seen in a pediatric practice in New Orleans, Louisiana, according to vaccination status against rotavirus, 1998–2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Month of birth</td>
</tr>
<tr>
<td>April 1998–August 1998</td>
</tr>
<tr>
<td>February 1999–June 1999</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Medical insurance</td>
</tr>
<tr>
<td>Medicaid</td>
</tr>
<tr>
<td>Health maintenance organization</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Median household income</td>
</tr>
<tr>
<td>≤$22,000</td>
</tr>
<tr>
<td>&gt;$22,000</td>
</tr>
<tr>
<td>No. of office visits</td>
</tr>
<tr>
<td>≤10</td>
</tr>
<tr>
<td>11–20</td>
</tr>
<tr>
<td>&gt;20</td>
</tr>
</tbody>
</table>

* Two-tailed chi-square analysis.
mate, after controlling for income and birth cohort, was 67 percent (95 percent CI: −48, 96).

Protection over time

Cases of rotavirus hospitalization occurred among the unvaccinated children during the three rotavirus seasons. Most of the cases (four of seven) occurred during the first season, when children were the youngest (attack rate: 1.18 per 100 child-years). In contrast, hospitalization of the partially vaccinated children was seen during the second season only, and no case occurred among fully vaccinated children during any of the three seasons (figure 2). The median age at hospitalization was 10 months (range: 7, 28) for unvaccinated cases, and the ages of the two partially vaccinated cases were 12 and 20 months, suggesting a delay in onset of severe rotavirus illness. No cases of intussusception or deaths were identified in the study cohort.

DISCUSSION

The study findings suggest that, in a clinical practice setting, routine rotavirus immunization prevented rotavirus-related hospitalizations to a degree similar to that shown by vaccine efficacy trials. Our point estimate for vaccine effectiveness was 70 percent, comparable to the 80 percent vaccine efficacy described in the literature for RRV-TV to protect against severe rotavirus disease (7). Since rotavirus testing was consistently performed only in hospitalized children, our study could not evaluate the impact of rotavirus vaccine in office or emergency department visits.

Our data suggest that full immunization was highly protective (100 percent) in preventing rotavirus hospitalization for 3 years. A study in Finland also showed that protection against severe disease persisted through three rotavirus seasons among fully immunized infants (22). The study findings also suggest that, although one to two doses of the vaccine may delay appearance of severe rotavirus illness, they are only partially protective (61 percent). The two partially immunized children who required hospitalization for rotavirus represented cases of missed opportunities, as sometimes occur in pediatric practice. One child received RRV-TV at 6 months (because the vaccine had just been made available) and 8 months of age and did not return for the third dose before 12 months of age. All immunizations for the second child started late (at 4 and 6 months of age), and RRV-TV was withdrawn before he was old enough to receive the third dose. These cases would suggest that the decrease in vaccine effectiveness was due mostly to vaccination failure rather than failure of the vaccine.

The rotavirus-related hospitalization rate among our unvaccinated children (1 in 65) is similar to the rate commonly cited by the Centers for Disease Control and Prevention (1 in 78) (1, 23). Still, our cohort was not large enough to enable us to detect sufficient cases of rotavirus hospitalization to attain statistical significance. For example, overall vaccine effectiveness was 70 percent with a 95 percent confidence interval of between −43 percent and 94 percent (table 2). A much larger cohort is required to narrow this confidence interval. We estimate that, on the basis of the incidence rate of rotavirus hospitalization that we found, a prospective cohort study would require over 4,000 subjects per group (vaccinated, unvaccinated) to detect a protective vaccine efficacy of ≥50 percent (with a power of 0.80 at a two-tailed significance level of 0.05) against severe rotavirus gastroenteritis. Such a sample size would be almost impossible to attain, since RRV-TV was withdrawn prematurely. A case-control study may be a suitable alternative.

Recognizing the limited statistical power of the data available for our study, we did not intend to test the hypothesis that RRV-TV was effective (i.e., protective effectiveness > 0) but rather to determine whether our point estimate of effectiveness would fall within the boundaries of efficacy reported in the literature. Since our point estimate for vaccine effectiveness (70 percent) indeed falls within the 95 percent confidence interval of vaccine efficacy (95 percent CI: 56–91) reported in the literature (7), our findings suggest that both estimates are similar. In other words, our results, by themselves, do not demonstrate whether RRV-TV is effective but rather—in conjunction with results from the literature—suggest that the effectiveness (real-life performance) of RRV-TV is similar to its efficacy (clinical-trials performance). We believe that the similarity in the estimates of vaccine effectiveness and efficacy is encouraging for future vaccine candidates and is likely a result of the simplicity of using this vaccine in practice, since it was administered orally at the time of regular infant visits and—at least for a period—was covered by Medicaid.

Even though our study group came from a single large practice, the participants seem representative of the children

### Table 2.

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>No. of doses received</th>
<th>No. of child-years*</th>
<th>No. of rotavirus hospitalizations</th>
<th>Attack rate (per 100 child-years)</th>
<th>Protective efficacy %</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>0</td>
<td>1,357</td>
<td>7</td>
<td>0.52</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1–3</td>
<td>1,303</td>
<td>2</td>
<td>0.15</td>
<td>70</td>
<td>−43, 94</td>
</tr>
<tr>
<td>Partially</td>
<td>1–2</td>
<td>1,000</td>
<td>2</td>
<td>0.20</td>
<td>61</td>
<td>−86, 92</td>
</tr>
<tr>
<td>Fully</td>
<td>3</td>
<td>303</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>−120, 100</td>
</tr>
</tbody>
</table>

† CI, confidence interval.
in the area. The birth cohort in New Orleans is estimated at 9,000 per year (24); 17 percent of the children are reported to have no insurance, 28 percent have Medicaid, and 55 percent have private insurance; and the median household income in Louisiana is $22,000 (21).

One potential limitation of our study is the rate of attrition: 22 percent of candidates were excluded; of those included, only 53 percent started immunization, and, of them, only 25 percent completed the three-dose series. We found no obvious difference between enrolled and excluded children except for insurance coverage, which might have accounted for the more reliable follow-up in the enrolled children (a criterion for enrollment); exclusion of these patients might have reduced the generalizability of our findings but was necessary to ensure that the groups were comparable regarding their chances of being offered RRV-TV and our chances of detecting rotavirus hospitalization. Similarly, we found no obvious difference between children who received vaccination and those who did not. Availability of the vaccine was not a problem and neither was reimbursement; the most common situation was parents refusing vaccination for their children. Practitioners presented the vaccine to parents as recommended (by the American Academy of Pediatrics) but not mandatory (by the state of Louisiana), and some parents opted not to accept the vaccine. Acceptance improved with time, but, unfortunately, the vaccine was withdrawn prematurely. Regarding the cases who did not complete vaccination, some represented missed opportunities and some refusals (as explained above), but most were young children who were not old enough to complete the series before use of RRV-TV ceased.

Another potential limitation of our surveillance system is that not all hospitalized children with gastroenteritis were tested for rotavirus, and it is uncertain how this problem could have affected the results. It is reassuring that, as noted above, the rate of rotavirus hospitalization detected in our study was similar to that commonly described in the literature. In addition, since all four untested children were unvaccinated, had any of them indeed tested positive for rotavirus, that result would have affected the protective efficacy in favor of the vaccine. In other words, if anything, our efficacy estimate represents the “worst-case” scenario. Finally, the vaccinated group had more overall office visits. Even though statistically significant, this finding is of uncertain meaning since the difference was small (two office visits) and unlikely to affect the chances of detecting rotavirus diarrhea. Even though there were some imbalances between vaccinated and unvaccinated children regarding birth cohort composition and maybe income, these variables did not appear to have a significant effect on our estimate of vaccine efficacy, since the adjusted and crude estimates (67 percent and 70 percent, respectively) were similar.

In conclusion, RRV-TV demonstrated high effectiveness against severe rotavirus disease when measured under real conditions of a clinical practice. Because vaccines are administered largely to healthy children, it is important that they are safe. In the United States, safe and effective rotavirus vaccines are needed to reduce the disease burden associated with emergency room visits and hospitalization due to severe rotavirus diarrhea and dehydration. In less developed countries, where mortality associated with severe dehydrating rotavirus gastroenteritis is high, the need remains for a vaccine with good protective efficacy against severe rotavirus diarrhea, a low risk of adverse side effects, and a favorable cost-effectiveness profile. Several additional rotavirus vaccines are currently in development (25). Our study findings support the potential health benefits that a safe and effective rotavirus vaccine might have in children in routine clinical practice. Further studies determining vaccine effectiveness rather than efficacy will provide public health officials and the public with a better measurement of the impact of a universal childhood immunization program against rotavirus and the characteristics that the appropriate vaccine should have.

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