Decline in Gastroenteritis-Related Triage Calls After Rotavirus Vaccine Licensure

WHAT’S KNOWN ON THIS SUBJECT: Rotavirus is a major cause of acute gastroenteritis among children worldwide. Vaccines targeting rotavirus have been demonstrated to be highly efficacious against severe disease in clinical trials and postlicensure studies. Vaccine impact on mild gastroenteritis has not been well studied.

WHAT THIS STUDY ADDS: We used a novel surveillance platform consisting of telephone triage data to capture mild gastroenteritis not detected in other surveillance systems. Since rotavirus vaccine licensure, gastroenteritis-related call proportions have declined, and peak gastroenteritis-related calls are correlated with community norovirus circulation.

abstract

OBJECTIVE: We sought to determine the impact of rotavirus vaccine implementation on gastroenteritis (GE)-related calls to a large telephone triage service in Tennessee.

METHODS: Total and GE-related calls received by the Vanderbilt Telephone Triage Program for children <5 years of age were examined from May 1, 2004 to April 30, 2010. Time series adapted Poisson regression models were used to compare weekly GE-related call proportions between the prevaccine (May 2004 to April 2007) and postlicensure (May 2007 to April 2010) periods. Separate models compared GE-related call proportions in the historical rotavirus (February to April) and nonrotavirus (May to January) seasons. Associations between call data and laboratory-confirmed rotavirus detections and regionally reported norovirus activity were also assessed.

RESULTS: There were 156,362 total calls and 19,731 GE-related calls. Annual GE-related call proportions declined by 8% (95% confidence interval, 3%–12%) in the postlicensure period; declines ranging from 23% to 31% occurred during the historical rotavirus season in all 3 postlicensure years. No declines occurred in the nonrotavirus season. After vaccine licensure, reductions in laboratory-confirmed rotavirus activity were associated with declines in GE-related call proportions. Peak GE-related call proportions in the postlicensure period occurred earlier than in prevaccine years and were not strongly associated with laboratory-confirmed rotavirus but instead showed good correlation with norovirus outbreaks.

CONCLUSIONS: A decline in GE-related call proportions among young children after rotavirus vaccine licensure was documented by using a novel surveillance platform that captures mild GE not detected in other surveillance systems. Since rotavirus vaccine licensure, peak call proportions correlate with regional norovirus activity, highlighting the role of that pathogen in community GE. Pediatrics 2012;130:e872–e878

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KEY WORDS: gastroenteritis, rotavirus, rotavirus vaccines, norovirus

ABBREVIATIONS: CDC—Centers for Disease Control and Prevention CI—confidence interval GE—gastroenteritis NREVSS—National Respiratory and Enteric Virus Surveillance System

All authors contributed to study concept and design, data acquisition, and/or analysis and interpretation of data, and participated in drafting and/or critical revision of the manuscript. All authors have approved the manuscript in its current form.


Accepted for publication May 23, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This work was supported by the Centers for Disease Control and Prevention and the New Vaccine Surveillance Network (5 U01 IP000022-05).
Rotavirus has long been recognized as a major cause of acute gastroenteritis (GE) among children worldwide.\(^1\) The development and licensure of rotavirus vaccines has the potential to greatly reduce this burden.\(^2\) Vaccine efficacy of 83% to 98% against severe laboratory-confirmed GE was demonstrated in randomized clinical trials of both licensed vaccines (Rotarix and RotaTeq) in Europe and the Americas.\(^3\)–\(^6\) In the United States, postlicensure studies of RotaTeq have demonstrated similar vaccine effectiveness against severe rotavirus GE of 87% to 100%.\(^7,8\) Several studies have also suggested that vaccine efficacy against milder disease may be less than for severe disease,\(^9,10\) but the actual impact of rotavirus vaccine on GE burden not necessitating clinic or emergency department visits has not been well studied.

By using data from a large electronic telephone triage system in Middle Tennessee, we sought to determine the temporal associations between rotavirus vaccine licensure and trends in GE-related calls for young children. We hypothesized that a decrease in the proportion of calls related to GE would occur after vaccine licensure beginning with the 2007–2008 rotavirus season, but that this decrease would be smaller than the previously reported declines in severe disease. We also hypothesized that the decline would primarily occur during the winter seasonal months when rotavirus occurs, and not during the summer months. Finally, we examined correlations between GE-related calls after vaccine licensure and regional norovirus surveillance data to estimate the contribution of norovirus to mild GE.

**METHODS**

This study was approved by the Institutional Review Board at Vanderbilt University.

**Data Sources**

**Telephone Triage Data**

The Vanderbilt Telephone Triage Program is a service available to health care providers in Middle Tennessee that offers after-hours telephone triage for pediatric patients and families. The program is staffed by registered nurses and uses an automated, protocol-driven triage tool based on chief complaint (LVM Systems, Inc., Mesa, AZ). When a call is received, triage nurses input data regarding caregiver report of chief complaint and illness severity and provide care recommendations based on standardized protocols. The protocols use drop-down menus with minimal free-text entry, allowing for efficient call indexing. For this analysis, we collected weekly call counts by age, practice, and chief complaint for children \(<5\) years of age from May 1, 2004 to April 30, 2010. GE-related calls were defined as those with a chief complaint of diarrhea alone, vomiting alone, or vomiting and diarrhea combined. All other calls were classified as non-GE calls. Total calls included both GE and non-GE-related calls.

**Rotavirus Laboratory Reports**

All positive rotavirus detections from the outpatient, emergency department and inpatient settings of Vanderbilt University Hospital are reported by the Vanderbilt Clinical Virology Laboratory to the National Respiratory and Enteric Virus Surveillance System (NREVSS). The NREVSS is a national laboratory-based system that monitors temporal and geographic patterns associated with the detection of select respiratory and enteric viruses. For this analysis, all laboratory-confirmed rotavirus detections reported by Vanderbilt to NREVSS from May 1, 2004 to April 30, 2010 were extracted from the national database at the Centers for Disease Control and Prevention (CDC).

**Norovirus Outbreak Surveillance Data**

Systematic outbreak surveillance data for suspected or confirmed norovirus GE were solicited by the CDC from 30 state health departments from January 1, 2007 to April 30, 2010.\(^11\) For this analysis, we used data from Tennessee and from bordering states that reported data (Arkansas, Alabama, Georgia, Kentucky, Missouri, and Virginia).

**Analysis**

**GE-Related Call Trends and Rotavirus Vaccine Licensure**

To account for potential secular changes that were not vaccine associated, we created an indicator of GE activity based on the proportion of all calls that were GE related. Data were analyzed as a time series of weekly GE-related call proportions as the outcome. We fitted time-series adapted Poisson regression models, controlling for seasonal variation by using a month indicator variable.\(^12\) The SE of the rate ratio was scaled to the Pearson \(\chi^2\) statistic divided by the residual degrees of freedom to account for overdispersion of the weekly proportions.\(^12\)

To estimate the impact of rotavirus vaccine licensure on GE-related call proportions, we calculated incidence rate ratios for the entire postlicensure period (May 1, 2007 to April 30, 2010) in comparison with the prevaccine period (May 1, 2004 to April 30, 2007), as well as for each of the 3 individual postlicensure years (May 2007 to April 2008, May 2008 to April 2009, and May 2009 to April 2010) in comparison with the prevaccine period. Although rotavirus vaccine licensure occurred in 2006, vaccine uptake in the 2007 rotavirus season was minimal.\(^8\) Thus, we considered this transitional year part of the prevaccine period. Separate models were also fitted for the historic rotavirus (February to April) and non-rotavirus seasons (May to January). To
Stata 10.0 (Stata Corp., College Station, TX) was used for all analyses. A 2-sided P value of < .05 was considered statistically significant.

RESULTS

There were 156,362 total calls representing 32 practices during the study period, including 19,731 (12.3%) GE-related calls (Table 1). Among the GE-related calls, 94.3% (annual range, 91.0%–95.7%) were advised home care, 1.9% (annual range, 1.5%–2.3%) were advised immediate evaluation in the emergency department, and disposition was not recorded for the remaining 3.8% (range, 1.8%–7.4% per year); no temporal trends were noted. The average weekly GE-related call proportions remained relatively stable throughout the study period (11.6%–12.9%), although weekly proportions varied widely during each year (range, 5.9%–25.6%), indicating strong seasonality of the GE-related calls. In the prevaccine period, mean weekly GE-related call proportions were highest in February (17.1%), March (19.2%), and April (15.9%), whereas, in the postlicensure period, the highest mean GE-related call proportions were of lesser magnitude and occurred slightly earlier in January (15.6%), February (15.4%), and March (12.6%).

Overall, GE-related call proportions declined by an estimated 8% (95% confidence interval [CI], 3%–12%) in the postlicensure period in comparison with the prevaccine period (Table 2). This trend was driven almost exclusively by decreased GE-related call proportions during the historical rotavirus season (28% overall decline; 95% CI, 22%–33%), with significant reductions observed in all 3 postvaccine years (23%–31%). To more accurately estimate the impact of rotavirus vaccine on GE-related calls, we also examined the correlation of GE-related call proportions with confirmed rotavirus positive detections from the Vanderbilt Clinical Virology Laboratory reported to NREVSS. GE-related call proportions peaked consistently in the late winter/early spring during the prevaccine period and correlated well with confirmed rotavirus activity (Fig 1). Reductions in confirmed rotavirus activity in the postlicensure years during this same time were associated with reduced monthly GE-related call proportions; the most substantial declines were noted in March (reductions of 28%–47%, P < .05 for all years) and April (reductions of 30%–46%, P < .05 for all years) (Fig 2A and B).

Overall, GE-related call proportions outside of the rotavirus season remained relatively stable in the postlicensure period in comparison with the prevaccine period, although significant increases were noted in 3 individual

### TABLE 1 Gastroenteritis-Related Triage Calls Among 32 Pediatric Practices in Middle Tennessee, May 2004 to April 2010

<table>
<thead>
<tr>
<th>Seasonal Year (May to April)</th>
<th>No. Practices</th>
<th>No. GE-related Calls</th>
<th>Total Calls</th>
<th>Mean Weekly GE-related Call Proportion (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevaccine period (2004–2007)</td>
<td>32</td>
<td>11,520</td>
<td>88,152</td>
<td>12.8 (5.9–22.5)</td>
</tr>
<tr>
<td>2004–2005</td>
<td>27</td>
<td>3,426</td>
<td>26,070</td>
<td>12.7 (7.1–21.8)</td>
</tr>
<tr>
<td>2005–2006</td>
<td>27</td>
<td>3,992</td>
<td>30,156</td>
<td>12.9 (7.8–22.4)</td>
</tr>
<tr>
<td>2006–2007</td>
<td>31</td>
<td>4,102</td>
<td>31,948</td>
<td>12.9 (5.9–22.5)</td>
</tr>
<tr>
<td>Postlicensure period (2007–2010)</td>
<td>31</td>
<td>8,211</td>
<td>68,210</td>
<td>11.9 (6.5–25.6)</td>
</tr>
<tr>
<td>2007–2008</td>
<td>31</td>
<td>3,822</td>
<td>32,311</td>
<td>11.7 (7.8–17.2)</td>
</tr>
<tr>
<td>2008–2009</td>
<td>28</td>
<td>2,087</td>
<td>16,626</td>
<td>12.2 (7.4–18.3)</td>
</tr>
<tr>
<td>2009–2010</td>
<td>24</td>
<td>2,032</td>
<td>19,073</td>
<td>11.8 (6.8–25.5)</td>
</tr>
</tbody>
</table>

GE-related calls included those with a chief complaint of diarrhea alone, vomiting alone, or vomiting and diarrhea. The denominator for the weekly GE-related call proportions included the total number of calls per week regardless of chief complaint. GE-related call proportions are expressed as percents. Prevaccine period defined as May 1, 2004 to April 30, 2007. Postlicensure period defined as May 1, 2007 to April 30, 2010.
postlicensure months: November 2008, December 2008, and January 2010 (Fig 2 A and B). This corresponded to a modest but statistically significant increase in GE-related call proportions during the nonrotavirus season in 2008–2009 (9% increase; 95% CI, 2%–16%) but not during other postlicensure years (Table 2). The timing of these increases also coincided with the peak GE-related call proportions in each year of the postlicensure period (November to February) and were not associated with confirmed rotavirus activity (Fig 1). Interestingly, GE-related call proportions during the 3 winter peaks observed in the postlicensure period coincided in both timing and magnitude with regional norovirus activity (Fig 2C). Comparing norovirus activity with modeled monthly nonrotavirus GE call proportions demonstrated moderate correlation overall ($r^2 = 0.53$). At the height of the winter peaks in the postlicensure years, norovirus was estimated to account for 40% or more of GE-related calls (Fig 2D).

**DISCUSSION**

In the first 3 years after rotavirus vaccine licensure, GE-related calls to a large telephone triage service in Middle Tennessee declined by nearly 30% during the historical rotavirus season. The reductions in GE-related calls coincided with the reduced number of laboratory-confirmed rotavirus detections from the Vanderbilt Clinical Virology Laboratory reported to NREVSS during this same period. GE-related calls outside of the rotavirus season remained largely unchanged, although small fluctuations were noted in individual years. Overall, there was an 8% reduction in GE-related call proportions in the postlicensure period in comparison with the prevaccine period. Peak GE-related call proportions in the postlicensure period occurred earlier (November to February) than would be expected from the traditional rotavirus season and were not associated with laboratory-confirmed rotavirus disease, but were associated with both the timing and magnitude of peak norovirus outbreak activity reported to CDC in Tennessee and surrounding states. This suggests that temporal shifts in rotavirus activity were not responsible for the observed winter peaks in the postlicensure period. Indeed, a previous study that examined temporal trends after rotavirus vaccine licensure suggested a several-week delay (rather than earlier onset) in seasonal rotavirus activity. The combination of these findings suggests that rotavirus vaccines were effective in preventing mild GE disease associated with telephone triage calls, and highlight the potential role of norovirus as an important cause of mild GE in the postlicensure period. Consistent with our findings,

### TABLE 2 Incidence Rate Ratios for GE-related Call Proportions After Rotavirus Vaccine Licensure

<table>
<thead>
<tr>
<th>Study Years (May to April)</th>
<th>Nonrotavirus Season, May to January, IRR (95% CI)</th>
<th>Rotavirus Season, February to April, IRR (95% CI)</th>
<th>All Year, IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevaccine period (2004–2007)</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Postlicensure period (2007–2010)</td>
<td>1.03 (0.98–1.08)</td>
<td>0.72 (0.67–0.78)</td>
<td>0.92 (0.88–0.97)</td>
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<tr>
<td>2007–2008</td>
<td>1.02 (0.95–1.09)</td>
<td>0.70 (0.63–0.79)</td>
<td>0.91 (0.86–0.97)</td>
</tr>
<tr>
<td>2008–2009</td>
<td>1.09 (1.02–1.16)</td>
<td>0.68 (0.62–0.78)</td>
<td>0.95 (0.90–1.02)</td>
</tr>
<tr>
<td>2009–2010</td>
<td>0.97 (0.91–1.05)</td>
<td>0.77 (0.69–0.86)</td>
<td>0.91 (0.85–0.97)</td>
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Prevaccine period defined as May 1, 2004 to April 30, 2007. Postlicensure period defined as May 1, 2007 to April 30, 2010. Incident rate ratios estimated by using Poisson regression. IRR, incidence rate ratio.
A recent study conducted in 3 US counties (including Davidson County, TN) that included population-based laboratory surveillance for norovirus among children with GE from October 2008 to September 2009 documented a substantial burden of norovirus among young children, with peak norovirus hospitalizations and emergency department visits occurring in the winter (December to February).\textsuperscript{14} Norovirus outbreaks largely occur among adults in long-term care facilities and are highly seasonal.\textsuperscript{11} Norovirus is also a common cause of adult hospitalizations due to acute GE.\textsuperscript{15,16} With reduced rotavirus transmission, it is possible that norovirus will become the principle driver of seasonal epidemics of childhood GE as well, and the good correlation with outbreak patterns suggests that triage call data may be a good syndromic system for signaling outbreak activity.

Declines in GE-related call proportions after vaccine licensure in our study were less than the reductions in severe disease previously demonstrated in the randomized clinical trials conducted in the developed world\textsuperscript{5–8} and reported in postlicensure studies in the emergency department and inpatient settings among similar populations.\textsuperscript{8,17} Both licensed rotavirus vaccines have been demonstrated to be more efficacious against severe than mild rotavirus GE.\textsuperscript{4,9,10,18} Moreover, rotavirus is a more common cause of acute GE among hospitalized children in comparison with outpatients, accounting for 50% and 27% of cases, respectively.\textsuperscript{19} Thus, smaller declines were expected when mild GE was the outcome and that was confirmed in our studies. However, because a proportion of vomiting and/or diarrhea calls may not have been caused by rotavirus or were noninfectious in nature (and therefore could not be prevented by vaccination) the impact of vaccine on mild rotavirus in the community may be underestimated when using GE-related calls as a proxy. Active surveillance of mild GE with laboratory confirmation of rotavirus is needed to more accurately assess the total vaccine impact on both mild and more serious disease.

Screening electronic data by using the chief complaint from health care encounters, including telephone triage calls, has previously been used to monitor the burden of influenza as well as to predict acute norovirus outbreaks.\textsuperscript{20–21} Similarly, trends in Internet search queries have also been shown to accurately predict both the timing and intensity of seasonal epidemics for these viruses,\textsuperscript{22–24} particularly for influenza (see: http://www.google.org/flutrends/). These novel approaches offer the potential for timely and efficient disease surveillance activities for prevalent conditions with strong seasonality. With additional refinement to include population-based estimates and validation against confirmed disease rates, data from large call centers such as the Vanderbilt Telephone Triage Program could potentially be used for real-time surveillance activities for

![Figure 2](image-url)
both acute gastrointestinal and respiratory illnesses. Moreover, although telephone triage services may not be immediately available in developing regions of the world, other low-cost data sources (eg, Internet search data) could be used in these settings to augment traditional surveillance of vaccine-preventable diseases.

Strengths of the current study include comprehensive access to an extensive call database that included >30 primary care practices serving children in Middle Tennessee over a 6-year period, the use of an indexed, protocol-driven electronic call triage system, and the availability of local active laboratory-based surveillance for rotavirus and statewide reporting of norovirus outbreaks in Tennessee and 6 bordering states. However, our study had several limitations, including the lack of a population denominator. As a result, although the use of GE-related call proportions may account for fluctuations in the number and size of practices using the call center over time, they are potentially sensitive to temporal fluctuations in total calls driven by other seasonal phenomena, such as influenza epidemics. Several approaches were considered to account for these fluctuations, including a Fourier analysis to "deseasonalize" non-GE calls, use of a long-term moving average, or use of total annual calls as the denominator. However, because the total call volume and number of participating practices varied in an irregular pattern, none of these approaches gave a signal as clear as the simple GE-related call proportions. In addition, we observed GE-related call proportions to be similar across primary care practices, suggesting that confounding due to differing practice participation over time was not an issue. The design of the telephone triage database also made it impossible to determine the rotavirus vaccination status of each of the symptomatic individuals. However, we know from active surveillance that vaccine coverage in Middle Tennessee increased rapidly during the postlicensure vaccine period. Similarly, it was not possible to determine the final diagnosis or assign etiology for each GE-related call, nor was it possible to determine the timing or course of illness for children using the triage system.

CONCLUSIONS

In summary, our study provides evidence of an observable decrease in mild GE in Middle Tennessee after rotavirus vaccine licensure. We also demonstrate that community norovirus activity may explain a large proportion of non-rotavirus GE episodes among young children during the winter season. In the postlicensure period, norovirus is likely to be an important cause of pediatric GE. Telephone triage data provide a novel surveillance platform for assessing mild GE that is not captured by other surveillance systems and offers much added information on the role of both rotavirus and norovirus disease patterns in the community.

REFERENCES


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*Pediatrics* 2012;130;e872; originally published online September 10, 2012;
DOI: 10.1542/peds.2012-0330

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