Multicenter Prospective Study on the Burden of Rotavirus Gastroenteritis in Turkey, 2005–2006:
A Hospital-Based Study

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Rotavirus is the main cause of gastroenteritis and dehydration requiring hospitalization among infants and children. Despite the high diarrhea-related mortality rate, there are limited studies describing the prevalence of rotavirus in Turkey. The disease burden of rotavirus gastroenteritis in Turkey was assessed by active, prospective surveillance conducted in accordance with a modified World Health Organization generic protocol from 1 June 2005 through 1 June 2006. A total of 411 children aged <5 years who were hospitalized for gastroenteritis in 4 centers were enrolled. Rotavirus was identified in 53% of samples from the 338 children tested; the range for individual centers was 32.4%–67.4%. Overall, 83.8% of rotavirus-positive children were aged <2 years. Rotavirus gastroenteritis occurred year-round but peaked in the winter. G1P[8] was the most widely prevalent strain (76% of strains), followed by G2P[4] (12.8%). G9P[8] was reported in samples from 3.9% of children. These data support the need for a rotavirus vaccine in Turkey.

Among all enteric pathogens that infect young children, rotavirus is the primary cause of severe gastroenteritis worldwide, affecting nearly all children by age 5 years and accounting for ≈39% (range, 29%–45%) of all diarrhea-related hospitalizations [3]. Although the incidence of rotavirus is similar in developing and developed countries, the mortality rate is higher in developing countries, likely because of poor access to hydration therapy and a high prevalence of malnutrition [1]. Global mortality due to rotavirus is estimated to be 527,000 deaths (range, 475,000–580,000 deaths) among children aged <5 years, with >80% of the deaths occurring in the developing countries of South Asia and sub-Saharan Africa [4,5].

Two vaccines (RotaTeq [Merck], licensed in the United States, Europe, and >69 countries worldwide, and Rotarix [GlaxoSmithKline Biologicals], licensed in the United States, Europe, and >100 countries worldwide) have demonstrated good safety, immunological, and efficacy profiles in large clinical trials conducted in western industrialized countries and in Latin America [6–12]. The WHO has given high priority to rotavirus
vaccination, and both Rotarix and RotaTeq have been pre-
qualified for use in developing countries [13, 14].

Epidemiological data on rotavirus disease burden are useful for
guiding rotavirus vaccination recommendations, including
assessment of the need for vaccination and the impact of the
vaccine in reducing the burden of rotavirus disease [15]. Nu-
merous reports have been published on the epidemiology of
rotavirus infection in various regions of the world, including
Europe and Middle East. However, few studies report the clini-
cal and epidemiological features of rotavirus gastroenteritis in
Turkey [15, 16], and other publications focus on the laboratory
diagnosis of rotavirus disease [17–19].

Turkey is a developing country with a population of 73 mil-
lion people and a diarrhea-associated mortality rate of 3.84
deaths per 1000 children aged <5 years [20]. A model described
by Parashar et al [1] projects 13,371,800 episodes of diarrhea
annually in Turkey among children aged <5 years, correspond-
ing to 94,817 hospitalizations and 1,182,046 outpatient visits.

The primary objective of this study was to estimate the propor-
tion of diarrhea-related hospitalizations attributable to ro-
tavirus among children aged <5 years who reside in Turkey,
with the use of local data as opposed to models extrapolated
from other sources. Other objectives included the determina-
tion of age and seasonal distribution of rotavirus hospitaliza-
tions and the identification of the prevalent rotavirus strains.

MATERIALS AND METHODS

Study design. This prospective, multicenter, hospital-based
study was conducted among children aged <5 years who were
hospitalized for gastroenteritis in 4 hospitals located in 4 major
cities in Turkey (Ankara, Istanbul, Izmir, and Adana); these
hospitals serve 37% of the population aged <5 years in Turkey.
Data were collected for a 12-month period from 1 June 2005
through 1 June 2006. The study design was based on the WHO
2002 generic protocol for hospital-based surveillance to esti-
mate the burden of rotavirus gastroenteritis among children
and was adapted on the basis of the country requirements [21].

The study was conducted in accordance with “good clinical
practice,” the 1996 version of the Declaration of Helsinki, and
local regulatory requirements and was approved by the local
ethics committee of each study hospital. Informed consent was
obtained from the parents or guardians of all eligible children.
This study was sponsored by GlaxoSmithKline Biologicals,
Belgium.

Inclusion and exclusion criteria. All children aged <5 years
who were hospitalized for gastroenteritis at the 4 study hospitals
were enrolled in the study. Gastroenteritis was defined by di-
arrhea (≥3 looser-than-normal stools per day) with or without
vomiting (≥1 episode of forceful emptying of partially digested
stomach contents ≥1 h after feeding per day). Children were
ineligible for inclusion if the diagnosis for treatment at the
study hospital did not include gastroenteritis or if the onset of
gastroenteritis was after hospitalization.

Data collection. The parents or guardians of the children
enrolled in the study were asked to complete a questionnaire
to collect information regarding the child’s demographic char-
acteristics, medical history, gastroenteritis episode, and area of
residence. The severity of gastroenteritis was assessed by the
investigators using the Vesikari scale [22]. Stool samples were
collected from all children who were able to provide them at
the time of recruitment and were tested for the presence of
rotavirus by enzyme-linked immunosorbent assay at the
GlaxoSmithKline Biologicals laboratory (Rixensart, Belgium).
All rotavirus-positive samples were tested by reverse-transcrip-
tase polymerase chain reaction for the VP7 and VP4 genes,
followed by a reverse hybridization assay at DDL Diagnostic
Laboratory (Delft, the Netherlands) to identify G and P types
[23].

Statistical analyses. The proportion of rotavirus gastro-
enteritis cases among all diarrhea-related hospitalizations of
children aged <5 years overall and by study center was com-
puted with exact 95% confidence intervals by using the total
number of children aged <5 years who were hospitalized for
gastroenteritis as the denominator. Statistical analyses were per-
formed using SAS, version 8.2 (SAS) [24].

RESULTS

A total of 411 children were hospitalized for gastroenteritis in
the 4 study hospitals and were assessed for rotavirus infection.
Of these children, 47 were excluded because they declined to
participate or did not sign the consent form, 2 were aged >5
years, and 1 received a diagnosis for treatment at the study
hospital that did not include gastroenteritis. The median age
of the 361 children enrolled in the study was 12 months (range,
0–60 months), 60.9% were male, and 91.7% lived in the same
city as the hospital to which they were admitted.

Stool samples were not available for 2 children. Of the 359
children with a stool sample, 15 had samples that were untested
or were insufficient in quantity, and 6 samples were lost, yield-
ing 338 children with stool samples available for analysis. The
overall proportion of rotavirus gastroenteritis among all chil-
dren hospitalized for gastroenteritis who were enrolled in the
study and were tested for rotavirus was 53% (179 of 338), with
the lowest proportion observed in Adana (32.4%) and the high-
est proportion observed in Izmir (67.4%) (Table 1).

Of the 179 children with rotavirus-positive stool samples,
83.7% were aged <2 years, 43.5% were aged <1 year, and 11.7%
were aged <6 months (Figure 1). Rotavirus gastroenteritis was
most frequently observed between October and April and
peaked in February (Figure 2). Of the 179 rotavirus-positive
stool samples that were available for typing, wild-type G1P[8]
was the most widely prevalent strain (76% of strains) (Figure
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Table 1. Proportion of Rotavirus Gastroenteritis among 338 Children Hospitalized for Gastroenteritis and Tested for Rotavirus

<table>
<thead>
<tr>
<th>Center</th>
<th>Total no. of children hospitalized for gastroenteritis and tested for rotavirus</th>
<th>Children who tested positive for rotavirus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percentage (95% CI)</td>
</tr>
<tr>
<td>Adana</td>
<td>105</td>
<td>34</td>
</tr>
<tr>
<td>İzmir</td>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td>Ankara</td>
<td>101</td>
<td>58</td>
</tr>
<tr>
<td>İstanbul</td>
<td>83</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>338</td>
<td>179</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval.

3), followed by G2P[4] (12.8%). G9P[8] was reported in samples from 3.9% of children.

Before hospitalization, 161 (89.9%) of 179 rotavirus-positive children and 133 (83.6%) of 159 rotavirus-negative children were reported to have had a “severe” episode of gastroenteritis, which was assessed using the 20-point Vesikari scale. Vomiting was reported in 165 (92.2%) of 179 rotavirus-positive children and 131 (82.4%) of 159 rotavirus-negative children. Severe dehydration was observed in 23 (12.8%) of 179 rotavirus-positive children and 13 (8.2%) of 159 rotavirus-negative children.

The median duration of hospitalization was 3 days, regardless of rotavirus status. During hospitalization, 164 (91.6%) of 179 rotavirus-positive children and 145 (91.2%) of 159 rotavirus-negative children received intravenous rehydration. Also, 16 (8.9%) of 179 rotavirus-positive children and 7 (4.4%) of 159 rotavirus-negative children had ongoing gastroenteritis during discharge from the hospital. One rotavirus-negative child, who received a diagnosis of juvenile myelomonocytic leukemia and febrile neutropenia, died during the study.

DISCUSSION

We estimated the burden of rotavirus among young children in Turkey, using a hospital-based surveillance study. Of the 338 children with samples available for laboratory confirmation, 53% tested positive for rotavirus, which is higher than previously reported proportions for rotavirus gastroenteritis in Turkey (39.8%, reported by Kurugol et al [15], and 36.8%, reported by Karadag et al [16]). Although this may reflect an increasing burden of rotavirus gastroenteritis in Turkey in recent years, the proportion of acute gastroenteritis hospitalizations attributable to rotavirus is dependent on the prevalence of other causes of diarrhea-related hospitalizations, which may vary over time. However, our estimates are comparable to results of more-recent hospital-based surveillance studies in Europe [25, 26].

In the Rotavirus Gastroenteritis Epidemiology and Viral Types in Europe Accounting for Losses in Public Health and Society (REVEAL) study, conducted in 7 European countries in 2004–2005, rotavirus accounted for 53.1%–68.8% of hospitalizations for acute gastroenteritis among children aged <5 years [25]. In the Surveillance for Hospitalised Rotavirus Infections in Kids (SHRIK) study, conducted in 12 hospitals in France, Germany, Italy, Spain, and the United Kingdom from February 2005 through August 2006, 56.2% of children aged <5 years who were hospitalized with acute gastroenteritis were found to be positive for rotavirus (range by country, 33.2%–64.4%) [26].

The proportion of rotavirus gastroenteritis varied between the study areas, ranging from 32.4% in Adana to 67.4% in İzmir. These regional differences may be because of differences in health care systems or cultural practices—for example, in some areas, children may have been more likely to be treated at home and not admitted to the hospital, which may have caused the proportion of rotavirus gastroenteritis cases to decrease [25, 26]. Because rotavirus gastroenteritis is treated mainly with oral rehydration, children with rotavirus gastroenteritis may be more likely to be treated at home than children with bacterial gastroenteritis, which may require antibiotic therapy.

Most of the rotavirus-positive children were reported to be aged <2 years in this study, which is consistent with the previous literature [15, 20, 25–27]. As in most countries with a temperate climate, rotavirus gastroenteritis was observed to have a clear seasonal pattern, peaking in the winter months between October and April and at the lowest levels during June and July.

In this study, wild-type G1P[8] was the most widely prevalent strain (76%), followed by G2, G4, and G9. These findings are similar to those reported for 2000–2001, in which G1 was the most common type (75.1%), followed by G2, G3, and G4 [15]. A review of 124 studies conducted from 1989 through 2004 in 52 countries found that strains with types G1, G3, and G4 in combination with type P[8] and strains with type G2 in combination with type P[4] were responsible for >88% of all ro-
tavirus infections worldwide [28]. In contrast to previous local studies [15], G9 (3.9% of strains) is reported to be an emerging type in Turkey. This is supported by the global review that detected type G9 in every continent, with an overall percentage of 4.1% [28]. Another recent Turkish study in Ankara conducted from September 2004 through December 2005 showed the overall prevalence of G9 to be 17.2% [29]. The authors described a shift of frequency of detection of G9 from 5.3% in 2004 to 17.4% in 2005, and 75% of the enrolled children in that study were outpatients [29]. Our data for inpatients, also in Ankara, showed that 57.4% were rotavirus positive, and only one G9P[8] strain was identified.

This study is the first, to our knowledge, to provide comprehensive information on the rotavirus disease burden for 4 major cities in Turkey. Its strengths include standardized study procedures, including enrollment of children at all participating hospitals. A potential limitation is the relatively low number of children hospitalized for gastroenteritis (411) and the fact that only 338 of these children provided stool samples for rotavirus analysis. It is possible that this may have introduced selection bias and that these 338 children may have had a different proportion of laboratory-confirmed rotavirus, compared with all children hospitalized for gastroenteritis. The overall proportion of rotavirus gastroenteritis calculated for all children hospitalized for gastroenteritis in this study (enrolled and non-enrolled children) was 43.6% (179 of 411).

Nevertheless, results of this study serve as good baseline information on the rotavirus disease burden in Turkey. The incidence of rotavirus disease is similar in both industrialized and developing countries, which suggests that improvements in water supply, hygiene, and sanitation may not adequately control the disease [3]. Effective immunization against rotavirus is an important public health measure and should be a priority in countries where disease burden, mortality, and morbidity are high. The introduction and universal application of rotavirus vaccine could provide a measurable and visible benefit to the health of a population within 2–3 years [30, 31] and will make a potentially positive contribution to the United Nations Millennium Declaration—which is to reduce the mortality rate among children aged <5 years by two-thirds by 2015 [32]. Turkey, where diarrheal diseases are the second most common infectious cause of childhood mortality [33], has the infrastructure and now has the supportive data to include a rotavirus vaccine in the national immunization program, in accordance with WHO recommendations.

Acknowledgments

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