Rotavirus: the guard dies, but it does not surrender

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Sir,

We read with interest a report in the present journal on rotavirus epidemiology 5–6 years after implementation in 2009 of a national immunization program in Finland [1]. Two live vaccines, Rotarix (GlaxoSmithKline) and RotaTeq (Merck & Co., Inc) were used and the vaccine coverage was over 90%. The authors concluded that rotavirus activity continues to persist, in vaccinated children aged 0–6 years and particularly in unvaccinated older children.

In Belgium, Rotarix was first introduced in 2006 and RotaTeq in 2007. Rotavirus vaccine has been partially funded and since November 2006 included in the Belgian national immunization program, with Rotarix being mainly used. We aimed to determine rotavirus prevalence and study rotavirus vaccine effectiveness in a Belgian pediatric population presenting to the Emergency Department for acute gastroenteritis, 10 years after rotavirus vaccine introduction.

The recruitment method and population have been previously described in details [2]. The study was approved by the ethical committees of the participating hospitals. Patients and their parents received information about the study before their participation and had to sign a written consent to participate.

Briefly, we recruited children presenting to the emergency department of two hospitals in Brussels with symptoms of acute gastroenteritis (cases) and age-matched controls from outpatient general pediatric clinics from the same hospitals, between May 2015 and October 2016. A questionnaire was completed during the emergency department visit, or later by phone, asking about patient’s medical history (chronic illnesses, rotavirus vaccination, medications, antibiotic treatment during the last six months, recent travel, school or daycare attendance, presence of other children at home, pets at home, specific diet) and about the current diarrheal episode (number of stools per day, presence of blood in stool, fever, nausea/vomiting, abdominal pain, treatment received, and the need for hospitalization). A telephone interview was also done one month after the emergency department visit to complete any missing data and establish the total duration of the acute gastroenteritis episode. The questionnaire that was administered to cases was administered to controls by telephone and an additional telephone call, one month later, established whether acute gastroenteritis had developed after stool sampling; if it did, the child was excluded.

To be considered valid, a rotavirus vaccine dose had to be administered at least 2 weeks before the recruitment date. For that reason, we excluded from the vaccine effectiveness analysis children less than 2 months and 2 weeks of age, as they were not considered protected.

Stools from cases and controls were analyzed for parasites (microscopy) and for common bacteria (culture method for Salmonella, Shigella, Yersinia, Aeromonas, Shiga Toxin Escherichia coli). Immunochromatographic methods were used to diagnose Norovirus (ImmunoCard STAT! Norovirus, Meridian Bioscience Inc, Cincinnati, USA), Rotavirus (Rotavirus strip, Coris Bioconcept, Belgium) and Adenovirus (Adenovirus 40/41 strip, Coris Bioconcept, Belgium).

Descriptive statistics and univariate analyses were performed. Chi-square and Fisher exact tests were used to compare pathogens prevalence in cases and controls. A p value <.05 was considered statistically significant. Univariate statistical analyses were done with Epi-info 7 version 7.2.1.0. Multivariate analyses using logistic regression were performed with STATA 13 (StataCorp. College Station, TX) to calculate rotavirus vaccine effectiveness (1-OR) and to analyze demographic and clinical characteristics in patients with acute gastroenteritis, rotavirus positive or negative.

During the study, 185 patients and 179 controls were recruited. Their baseline characteristics were similar (Table 1), but no rotavirus test was done in 3 cases and 1 control.
Table 1. Description of cases and controls recruited in the study.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>185</td>
<td>179</td>
</tr>
<tr>
<td>Median age</td>
<td>18.9</td>
<td>19.73</td>
</tr>
<tr>
<td></td>
<td>IQR 34.6 months</td>
<td>IQR 33.8 months</td>
</tr>
<tr>
<td>Female</td>
<td>83/185 (44.9%)</td>
<td>82/179 (45.8%)</td>
</tr>
<tr>
<td>Rotavirus vaccine</td>
<td>120/149 (80.5%)</td>
<td>123/152 (80.1%)</td>
</tr>
<tr>
<td>Antibiotic treatment during last 6 months</td>
<td>41/161 (25.5%)</td>
<td>52/175 (29.7%)</td>
</tr>
<tr>
<td>Travel outside Europe</td>
<td>7/168 (4.2%)</td>
<td>2/178 (1.1%)</td>
</tr>
<tr>
<td>Occupation : day care</td>
<td>47/168 (28.0%)</td>
<td>53/178 (29.8%)</td>
</tr>
<tr>
<td>Home</td>
<td>77/168 (45.8%)</td>
<td>75/178 (42.1%)</td>
</tr>
<tr>
<td>School</td>
<td>44/168 (26.2%)</td>
<td>50/178 (28.1%)</td>
</tr>
</tbody>
</table>

No rotavirus were diagnosed in controls; 20 cases were rotavirus positive (20/182, 11%). It was the second most prevalent enteric pathogen after *Campylobacter jejuni* in our study.

In cases, rotavirus infection was associated, when adjusted for potential confounders (sex, white blood cells in stools, co-infection, medical history, other children at home with or without diarrhea, school and day-care attendance, antibiotherapy during the last 6 months), with the presence of fever (adjusted odds ratio [aOR] 6.6; 95% CI: 1.20–124.07) and with nausea/vomiting (aOR 11.5; 95% CI: 2.1–219.8).

Vaccine information was not available for 28 cases and 20 controls. The study population for the vaccine effectiveness analysis was therefore 143 cases: 15 were rotavirus positive and 118 were vaccinated (82.5%) and 150 controls: none were rotavirus positive and 123 were vaccinated (82.0%). The overall vaccine effectiveness was 57.9% (95% CI: –29.5%, 86.3%). The adjusted vaccine effectiveness for children <3 years was 59.7% (95% CI: –51.1, 88.6), adjustment was done for the same potential confounders previously listed. When stratified by age group (Table 2), the proportion of rotavirus-positive children was different between vaccinated and unvaccinated, especially in children less than 12 months of age, where rotavirus cases were significantly more frequent in unvaccinated than in vaccinated children. That effect seemed present in the 12–24 months but was not statistically significant.

Despite rotavirus vaccination, rotavirus remains an important pathogen in pediatric gastroenteritis in Belgium, associated with 11% of diarrheal episodes, often associated with fever and nausea. Vaccine effectiveness was not statistically significant in our study considering the low prevalence of rotavirus-positive patients. However, in children less than one year old, there were statistically more rotavirus cases (4/41) in non-vaccinated than in vaccinated (0/64) patients (p = .01, Table 2). The same trend seems present in the 12–24 months old group, but sample size and a high overall vaccination coverage is a limitation.

Table 2. Proportion of cases of rotavirus acute gastroenteritis in vaccinated and unvaccinated children according to age.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>0/64 (0%)</td>
<td>4/41 (10%)</td>
<td>.01</td>
</tr>
<tr>
<td>12–24 months</td>
<td>3/72 (4%)</td>
<td>1/12 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>7/105 (7%)</td>
<td>0/18 (0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

In the post-vaccine era, the role of rotavirus in milder disease, for example as a cause of community consultation, has been less studied. Studies focusing on the outcome, such as emergency department visits and general practitioner consultations, are required because this is likely the greatest burden of rotavirus on healthcare resources in high-income countries [3]. In the post rotavirus vaccine era, United States data showed a relative reduction in the rates of outpatient visits (1–24%, according to year, age of the patient and time of the year) and emergency department visits (4–28%, according to year, age of the patient and time of the year) for all causes acute gastroenteritis in children one year old or less but not clearly in older children [4]. Across Europe, rotavirus vaccine effectiveness against rotavirus-related health care utilization varies from 68–84% [5]. Outpatient visits significantly decreased after the introduction of rotavirus vaccine (vaccine effectiveness =50–83%), even if vaccine was more effective in preventing rotavirus-related hospitalization (vaccine effectiveness =80–98.3%) [5]. In England, rotavirus vaccine was estimated to decrease the number of acute gastroenteritis seen in general practice by 15% overall and by 41% in a month with historically high rotavirus circulation [6]. In Belgium, rotavirus was responsible for ~16% of admission for acute gastroenteritis in young children, compared to 58% in the pre-vaccine era [7].

The present work shows that, despite a relatively high vaccine coverage of more than 80%, rotavirus is still the etiology of about 10% of acute gastroenteritis leading to an emergency department visit for children. This cannot be explained only by vaccine coverage: in patients presenting with an acute gastroenteritis rotavirus + for whom vaccine information was available, 10/15 were vaccinated. However, when looking at patients’ age, among the 10 vaccinated acute gastroenteritis rotavirus + patients, 8 were older than 2 years while the oldest of the 5 acute gastroenteritis rotavirus – patients was 1.6 years old. This age distribution could be the result of a decrease in vaccine effectiveness with time [8]. A possible selection of certain serotypes following intensive use of monovalent rotavirus vaccine has been raised,
and it is thus warranted to monitor circulating serotypes over the years [9,10].

This work is a secondary analysis of the collected database. This explains the low power and limitation due to the small number of rotavirus + cases. The post-hoc power obtained for our data is 35%. The fact that vaccination status was reported by parents, without verification of the vaccination booklet or of a vaccination registry, is another limitation of this work. Even with two study sites, the population was quite similar, arising from the low and middle socio-economic classes of Brussels, which may decrease the generalizability to other non-urban populations.

Despite a good overall vaccine coverage, rotavirus is still responsible for about 10% of acute gastroenteritis in a pediatric population in Belgium, leading to emergency department visits and imposing costs to the health care system and to society. Rotavirus acute gastroenteritis is associated with frequent fever and vomiting. The role of rotavirus in milder acute gastroenteritis has to be monitored and vaccine coverage can still be optimized to better protect children less than 12 months.

**Acknowledgments**

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**Disclosure statement**

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**References**


