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Effectiveness of rotavirus vaccination in Spain

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With the aim of determining rotavirus vaccine effectiveness (RVVE) in Spain, from October 2008/June 2009, 467 consecutive children below 2 years old with acute gastroenteritis (AGE) were recruited using a pediatric research network (ReGALIP, www.regalip.org) that includes primary, emergency and hospital care settings. Of 467 enrolled children, 32.3% were rotavirus positive and 35.0% had received at least one dose of any rotavirus vaccine. RVVE to prevent any episode of rotavirus AGE was 91.5% (95% CI: 83.7%–95.6%). RVVE to prevent hospitalization by rotavirus AGE was 95.6% (85.6–98.6%). No differences in RVVE were found regarding the vaccine used. Rotavirus vaccines have showed an outstanding effectiveness in Spain.

Introduction

The effectiveness of the rotavirus vaccine has been examined in different ecological and post-marketing studies, mainly coming from the US and related to the pentavalent vaccine.[1-3] In Spain both the monovalent (Rotarix™-GlaxoSmithKline) and pentavalent (Rotateq™-Merck/sanofi pasteurMSD) rotavirus vaccine are available since 2007. The Vaccine Advisory Board of the Pediatric Spanish Association (AEP, www.aeped.es) recommended universal immunization against rotavirus and included this vaccine in the recommended child inmmunization schedule in 2008, although it is not reimbursed by the healthcare system.[4,5] We have prospectively estimated the effectiveness of rotavirus vaccination in Spain.

Results

The study was offered to 505 children under 2 years old: 12 rejected to participate and 26 did not complete the study and/or were withdrawn because of missing data in any of the study endpoints. Finally 467 patients suffering acute gastroenteritis with a mean age of 12.2 ± 6.3 months were included. 151 (32.3%) were caused by rotavirus and 163 (35.0%) had received at least one dose of rotavirus vaccine (56.4% received monovalent vs. 43.6% pentavalent vaccine) (**Table 1**). Mean duration of the episode was 7.6 ± 3.6 days with a maximum number of bowel motions per day of 7.1 ± 3.6. Each child required a mean of 2.1±1.2 medical visits during the disease, and 130 patients (27.8%) required hospital admission, with a mean stay of 4.6 ± 2.1 days. Patients with rotavirus acute gastroenteritis (RAGE) were admitted to hospital more frequently (50.3% vs. 17.1%, $p < 0.001$).

Rotavirus vaccination effectiveness (RVVE)—after receiving at least one dose of either vaccine—was 91.5% (95% confidence interval: 83.7%–95.6%) to prevent any episodes of RAGE and 95.6% (85.6%–98.6%) to prevent hospital admission due to RAGE (**Table 2**). There were no significant differences in vaccine effectiveness regarding the type of vaccine used: monovalent and pentavalent RVVE against RAGE hospitalization were 97.5% (81.5–99.6%) and 92.9% (70.0–98.3%), respectively. RVVE was higher when only children fully vaccinated were considered for the analysis: 98.3% (87.4–99.8%). No differences were found in RVVE in fully vaccinated children depending on the vaccine applied (**Table 2**). RVVE in children partially vaccinated although smaller was significant: 84.0% (45.5%–95.3%) to prevent any episodes of RAGE and 89.4% (53.9%–97.5%) to prevent hospital admission due to RAGE. The rest of effectiveness estimations are summarized in **Table 2**.

Discussion

According to our results, immunization against rotavirus with either monovalent or pentavalent vaccine was highly effective in preventing any episode of acute gastroenteritis due to rotavirus. This protection is apparent from the first dose of vaccine, although the effectiveness is substantially lower than that achieved after completing the vaccine schedule.

Our results are consistent with those reported for Europe, US and Latin America.[1-3,6-8] The pentavalent rotavirus vaccine had

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Table 1. Summary of patient characteristics

	GLOBAL (All etiologies) (n = 467)	Gastroenteritis by rotavirus (n = 151)	Gastroenteritis by other etiologies (n = 316)	p
Age (months)				
0–6 months	103 (22.1%)	28 (18.5%)	75 (23.7%)	0.390
7–12 months	131 (28.1%)	42 (27.8%)	89 (28.2%)	
13–24 months	233 (49.9%)	81 (53.6%)	152 (48.1%)	
Sex (male %)	267 (57.2%)	91 (60.3%)	176 (55.7%)	0.351
Rotavirus vaccination				<0.001
No	304 (65.1%)	140 (92.7%)	164 (51.9%)	
Complete	138 (29.6%)	8 (5.3%)	130 (41.1%)	
Partial*	25 (5.4%)	3 (2.0%)	22 (7.0%)	
Maximum number of depositions in 24 hours	7.1 ± 3.6	8.4 ± 4.1	6.5 ± 3.2	<0.001
Gastroenteritis episode duration (days)	7.6 ± 3.6	7.6 ± 3.0	7.5 ± 3.9	0.172
Hospital admission	130 (27.8%)	76 (50.3%)	54 (17.1%)	<0.001
Length of hospital stay (days)	4.6 ± 2.1	4.6 ± 2.1	4.5 ± 2.2	0.519

(*) Represents those children that received at least one dose of either vaccine.

Table 2. Summary of estimated rotavirus vaccine effectiveness in children below 2 years of age expressed as % (95% CI)

	Effectiveness to prevent any episode of rotavirus gastroenteritis in:	Effectiveness to prevent hospitalization by rotavirus gastroenteritis in:
- Children 0–2 years old that have received at least one dose of either vaccine	**91.5% (83.7–95.6%)**	**95.6% (85.6–98.6%)**
(a) Only those with monovalent vaccine#	96.0% (87.2%–98.8%)	97.5% (81.5%–99.6%)
(b) Only those with pentavalent vaccine#	85.1% (67.9%–93.1%)	92.9% (70.0%–98.3%)
- Children 0–2 years old fully vaccinated with either vaccine	**92.8% (84.7%–96.6%)**	**98.3% (87.4%–99.8%)**
(a) Only those with monovalent vaccine#	97.2% (88.6%–99.3%)	97.3% (80.6%–99.6%)
(b) Only those with pentavalent vaccine#	84.4% (62.3%–93.5%)	95.0% (63.1%–99.3%)
- Children 0–2 years old partially vaccinated with either vaccine*	**84.0% (45.5%–95.3%)**	**89.4% (53.9%–97.5%)**
(a) Only those with monovalent vaccine#	43.8% (-411.2%–93.8%)	70.7% (-165.1%–96.8%)
(b) Only those with pentavalent vaccine#	87.5% (4.7%–98.4%)	87.0% (42.9%–97.0%)

*Those children that have received only one dose of the monovalent rotavirus vaccine, or one or two doses of the pentavalent rotavirus vaccine.
This data is only informative. The study was not designed to assess differences in effectiveness of individual vaccines and sample size is too small. See text for further explanations.

shown a high efficacy in Europe, with a reduction in the rate of either hospitalizations or emergency department visits due to acute rotavirus gastroenteritis of 94.5% for up to 2 years after vaccination.[6] The effect of rotavirus universal mass vaccination in the Austrian population one season after vaccine introduction showed a 74% reduction in hospitalization due to RAGE with an average vaccine coverage of 72%.[7] More recent data coming from Belgium—where both vaccines are available with about 80% government subsidization of the public price—revealed a 66% reduction in the percentage of rotavirus positive cases out of all hospitalized gastroenteritis cases tested.[8] Our estimated rotavirus vaccine effectiveness is much higher than that observed in low income countries; the reasons for such differences, although not fully understood, might be related with factors such as malnutrition, breast milk antibodies interference or the interaction of other enteric pathogens, among other factors.[9-11]

In our study, the vaccine effectiveness against any episode of rotavirus acute gastroenteritis regardless its severity was remarkably high, and not significantly different than that estimated for prevention of hospitalization due to rotavirus—the main outcome

considered in rotavirus clinical trials. A potential explanation for this might be the over-representation of severe cases, however the recruiting network included both primary, emergency room and hospital care patients. In Spain most pediatric emergency rooms of hospitals function as continuous care points and the population seen there does not differ from that of primary care. Also, the hospitalization rate in our series matches previously reported rates for Spain.[12,13] Only long term surveillance and population community-based database systematic studies might corroborate this finding. If this was the case, the impact of vaccine effectiveness in vaccination efficiency would be of great importance.

In Spain, rotavirus G-types G_1–G_4 and G9 represented >99% of circulating rotaviruses.[4,5] Universal rotavirus vaccination with any of the available vaccines is recommended by the Pediatric Spanish Association since 2008.[4,5] However, none of the vaccines is reimbursed and parents will fully cover vaccine cost: 200.50 euros for the 3 doses of Rotateq® or 181.20 euros for the 2 doses of Rotarix® (GSK). Like in our study, each vaccine available accounts for approximately half of the market. The effectiveness of both vaccines was comparable for rotavirus hospitalization prevention anytime the child completed the vaccination schedule. The effectiveness of partial vaccination was smaller in those receiving 1 dose of the monovalent vaccine compared to 1 or 2 doses of the pentavalent vaccine; however the reduced sample size precludes any definite conclusion on this point. Our study was not designed and/or powered to assess differences in effectiveness between vaccines.

The mean estimated rotavirus vaccination coverage in Spain in 2009 was 40%, assuming that all children receive the complete vaccination schedule. This coverage is calculated according to the number of distributed doses of each vaccine per year (Source: IMS Health) divided by 2 or 3 doses depending on the vaccine used, and by the registered number of children under 1 year of age born for that same period (Source: Spanish National Statistics Institute). In the Spanish region of Galicia, that estimated coverage of vaccination was 12% between July 2006 and June 2007, 43% between July 2007 and June 2008 and 51% between July 2008 and June 2009. In the present study only 34.9% of recruited children had received at least one vaccine dose. This difference between the estimated vaccine coverage for our study population (51%) and that found in our sample could be explained by the high vaccine efficacy itself that led to a dramatic reduction in the need of any kind of medical attention due to acute gastroenteritis in those children vaccinated. If this is considered, the actual vaccine effectiveness may even be underestimated in our study.

The vaccine failures detected in our study should be interpreted with caution: they where few and only one required hospital admission. Besides, only fecal immunoassay for rotavirus detection was performed in each patient and thus, co-infection cannot be excluded.

There are some limitations to our study: the slightly smaller than expected proportion of rotavirus cases, the multicentre nature of the study and the high hospitalization rate that might oversize hospitalized population.[12,13] The previous experience of the main team with a similar protocol,[14] the specific training of the participant subinvestigators distributed throughout the region and using the same methodology during the same study period, and the conservative approach applied make our results and conclusions highly consistent and representative.

In conclusion, both rotavirus vaccines seem to have an outstanding effectiveness in Spain. We believe that these encouraging results should be taken into account in rotavirus vaccine policies and inform practical recommendations from both the individual and the public health perspectives, namely, its official recommendation and universal availability free of charge for all infants.

Material and Methods

A prospective, observational multicentre study was conducted from October 2008 through June 2009 using a pediatric research network (ReGALIP, www.regalip.org) that includes primary, emergency and hospital care settings. Any patient up to 5 years old seeking care because of an acute gastroenteritis (AGE) episode was considered eligible for the study provided that they fulfilled the following conditions: (a) three or more bowel motions less consistent than usual, whether associated to vomiting or not, in a 24-hour period; (b) symptoms must have occurred within 7 days of enrollment, preceded by a 14-day symptom-free period; (c) an episode of acute gastroenteritis must not have occurred in the two weeks prior to the onset of current symptoms. Clinical and epidemiological data were recorded. Vaccination date and number of doses received were also registered and verified through the patient's vaccination record. Also non-medical expenses incurred throughout the episode were collected in detail as an independent part of the project (see www.rotacost.org for detailed information). At least one fecal immunoassay for rotavirus detection in a fecal sample was performed in all included patients (VIKIA Rota-Adeno®, Biomerieux). The stool specimens were obtained in the inclusion visit, either provided by the parent in the diaper or through a plastic adhesive bag or obtaining a sample with a rectal swab.

Only the data obtained from those patients under 2 years of age at inclusion and thus eligible for vaccination against rotavirus during the study period, were analyzed in this study. A descriptive analysis of AGE episodes was performed. Results are shown as frequencies and percentages or mean ± standard deviation, as needed. Differences between episodes of acute gastroenteritis positive and negative to rotavirus were assessed with the chi-squared test and the Mann-Whitney test for qualitative and quantitative variables, respectively. Crude odds ratios (OR) were calculated from the comparison of the frequency of rotavirus vaccination in patients with any episode of acute gastroenteritis positive and negative to rotavirus etiology, respectively. Rotavirus vaccine global effectiveness was estimated as *1-odds ratio*, with its 95% confidence interval. Rotavirus vaccine effectiveness (RVVE) to prevent hospital admission due to rotavirus AGE (RAGE) was also calculated in the same manner. These estimations were calculated for children below 2 years old, those eligible to have received rotavirus vaccine. Any patient receiving at least one dose of either vaccine was considered partially vaccinated. Any patient having received a full series of either vaccine (either 2 doses of monovalent vaccine or 3 doses of pentavalente vaccine)

Table 3. Summary of characteristics of potential vaccine failures

Patient	Age (months)	Gender	Rotavirus vaccination	Gastroenteritis episode duration (days)	Hospital admission	Length of hospital stay (days)	Maximum number of depositions in 24 hours
1	8	Male	Fully vaccinated, monovalent vaccine	4	No	-	8
2	20	Male	Fully vaccinated, monovalent vaccine	10	No	-	4
3	15	Male	Fully vaccinated, pentavalent vaccine	3	No	-	4
4	8	Female	Fully vaccinated, pentavalent vaccine	3	No	-	2
5	9	Female	Fully vaccinated, pentavalent vaccine	3	No	-	9
6	16	Male	Fully vaccinated, pentavalent vaccine	8	No	-	10
7	17	Male	Fully vaccinated, pentavalent vaccine	14	No	-	5
8	16	Female	Fully vaccinated, pentavalent vaccine	8	Yes	6	5

Vaccine failure was defined as a patient having received a full series of either vaccine and presenting AGE by rotavirus.

and presenting AGE by rotavirus was considered a potential vaccine failure (**Table 3**).

Statistical analysis was performed by using SPSS 17.0 for Windows. A p value below 0.05 was considered significant. This study was approved by the reference ethics committee. All parents or guardians received information about the study and signed an informed consent before study entry.

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Authors' Contributions

F.M.T., M.B.A., L.R.C., J.S.L. and J.M.S. conceived the study, participated in its design and coordination, and helped to draft the manuscript. F.M.T. created and directed the network. M.B.A. did the main field work. All authors read and approved the final manuscript.

Potential Conflict of Interest

Dr. F. Martinón-Torres has received research grants and/or honoraria as consultant/advisor and/or speaker from GlaxoSmithKline, sanofi pasteur MSD, Pfizer Inc., Wyeth, Novartis and Medimmune Inc.

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