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A Matched Case-Control Study Measuring the Effectiveness of the Rotavirus Vaccines to Prevent Gastroenteritis Hospitalizations

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Abstract

Rotavirus has been identified as an important cause of diarrhea hospitalizations. Two oral live rotavirus vaccines have been licensed in Europe since 2006 and have been available in the Spanish market since then. The main objective of this study was to estimate the effectiveness of the rotavirus vaccination in the prevention of admissions caused by rotavirus infections using a matched case-control study in a hospital setting.

Patients and methods: Prospective, hospital based, matched case-control study including patients between aged between 2 months and 5 years, hospitalized during 2008-2010 with a diagnosis of Rotavirus Acute Gastroenteritis (RV+AGE) matched against two patients diagnosed as Rotavirus negative Acute Gastroenteritis (Control group A) and five patients hospitalized with non-gastrointestinal conditions (Control group B) (i.e. in the ratio 1:2:5).

Results: 466 patients were included: 57 cases of RV+AGE, 104 patients in Control group A and 305 in Control group B. No differences were found among the 3 groups when comparing demographic data. Vaccine effectiveness was estimated as 86% (95% CI 59-95) compared to group A and 88% (95% CI 68-95) compared to group B. Prior rotavirus vaccination was more frequent in mild cases than in those with moderate-severe symptoms and the length of admission was shorter in vaccine recipients (1.7 ± 0.8 days) compared to those non-vaccinated (3.2 ± 1.4 days) (p<0.001; 95% CI: 1.3-1.7).

Conclusions: Our study found the rotavirus vaccines to be highly effective in preventing rotavirus-related hospitalizations and to reduce the severity of the rotavirus disease.

Introduction

Rotavirus is the most common cause of severe acute gastroenteritis in infants and young children worldwide [1]. In Europe, several studies have identified Rotavirus as an important cause of diarrhea hospitalizations producing a vast number of admissions, especially in winter months, coinciding with the influenza and Respiratory Syncytial Virus seasons. The greatest disease burden is found in children aged <2 years [2-4]. In Spain, rotavirus has been estimated to account yearly for approximately 181,626 Rotavirus Acute Gastroenteritis (AGE) episodes among children, including 14,342 hospitalizations, 41,701 emergency room visits, and 48,320 outpatient visits [5]. The annual costs of Rotavirus AGE in children <5 years of age have been estimated at €28.6 million from the National Health System perspective while, from the societal perspective, they were estimated at €50.0 million.

The World Health Organization (WHO) has recommended the inclusion of rotavirus vaccines into all national immunization programmes [6,7]. Two oral live rotavirus vaccines, Rotarix (human monovalent vaccine containing genotype G1P [8] developed by GlaxoSmithKline, Brentford, United Kingdom) and RotaTeq (human-bovine pentavalent vaccine containing G1-4 and P [8] developed by Merck, Whitehouse Station, NJ) have been licensed in Europe since 2006 and have been available in the Spanish market since then. However, concerns regarding the laboratory finding of fragments of a circovirus in rotavirus vaccines lead the Spanish Agency of Medicines to issue a ban on these in 2010 that still stands for Rotarix, despite the fact that no adverse events of clinical importance in humans have been identified in association with these findings, and that both vaccines have demonstrated good safety and efficacy profiles in large clinical trials, in accordance with WHO, EMA (European Medicines Agency) and FDA (Food and Drug Administration) recommendations [7].

A significant reduction in the incidence of childhood diarrhea leading to hospitalization has been reported after the introduction of either routine childhood rotavirus vaccination or targeted vaccination recommendations in several countries, including Spain [8-10]. Despite the availability of rotavirus vaccines and convincing results from clinical trials and ecological studies, by 2013 only a small number of European countries had introduced routine rotavirus vaccination in the recommended childhood immunization schedule. In Spain, this policy has not been adopted for the public health service, but several

medical societies recommend its administration, and it is implemented in the private market [11,12]. These facts lead to difficulties in the assessment of rotavirus vaccines uptake and of their effects on the population. Moreover, recent data suggest that rotavirus vaccine effectiveness may vary by geographic region [13]. In Europe, some differences in epidemiological characteristics of rotavirus infections have been reported [14]. Thus, studies monitoring rotavirus effectiveness post-marketing, under conditions of routine use, are essential to inform vaccination policies.

With rotavirus vaccines increasingly being introduced into childhood immunization programs, monitoring effectiveness in real life settings is a high priority and has been requested by the European Medicines Agency. The main objective of this study was to estimate the effectiveness of rotavirus vaccination in the prevention of admissions caused by rotavirus infection using a matched case-control study in a hospital setting.

Patients and Methods

Prospective, hospital based, matched case-control study including patients between aged between 2 months and 5 years, hospitalized during 2008-2010 with a diagnosis of Rotavirus AGE (RV+AGE). Every patient was matched against two patients diagnosed as Rotavirus negative AGE (RV-AGE) (Control group A) and five patients hospitalized with non-gastrointestinal conditions (Control group B) (i.e. in the ratio 1:2:5). The minimum sample size was calculated based on 90% power, 0.05 alpha value, a hypothetical vaccine effectiveness of 80%, and an estimated 40% vaccine coverage (based on sales reported from IMS Health). With these parameters, the minimum sample size needed was 46 cases. All controls were matched by age and birth date (with a maximum of 8 weeks difference), gender, and same date of admission. Rotavirus cases were diagnosed in stool samples tested using a commercial enzyme immunoassay (EIA) collected within 3 days of admission. Demographic data, cohabiting siblings, clinical findings using the Ruuska-Vesikari scale (calculated with data available for the full duration of the episode of gastroenteritis) as previously described [15], Past medical history and vaccination schedule were analyzed. Immunization data were obtained from medical records. Parents were interviewed and asked to provide immunization information for those patients whose records did not include it. Rotavirus vaccination status was classified as positive with at least one dose administered. Institutional Review Board approval was obtained from the local Research Committee.

Data were analyzed by bivariant logistic regression using the computer programs SPSS version 17.0. Statistical significance was defined as $P < 0.05$, all P values were 2-sided. Vaccine effectiveness was calculated as follows: $VE = (1 - \text{Odds Ratio}) \times 100$. Cases that had received their first rotavirus vaccination <14 days prior to the onset of rotavirus symptoms were excluded from the analysis. For controls, vaccine doses given <14 days before the date of their matched case's symptom onset were not included.

To estimate the coverage of the rotavirus vaccines, sales in the hospital's area of influence were obtained from IMS Health. The expected number of vaccinees was obtained by dividing the total doses by 2 or 3 doses depending on the vaccine used. Coverage was then estimated by dividing the estimated number of vaccinees by the registered number of children under 1 year of age born in that same period in the catchment area of our hospital.

Results

During the study period, a total of 466 patients were included: 57 cases of RV+AGE, 104 patients in control group A (RV-AGE) and 305 in Control group B. The average age for all the cases and controls were 13.07 ± 9.62 months and 59.2% were males. No differences were found among the 3 groups when comparing age, sex, prematurity (gestational age <37 weeks), breastfeeding, cohabiting siblings, and country of origin of parents, (Table 1). Most cases of RV+AGE were found in 2008 (56%) compared to 2009 (23%) and 2010 (21%) (p<0.001). RV-AGE cases were equally distributed among 2008 (33%), 2009 (38%) and 2010 (29%). On analysing the severity of AGE in cases and A group controls, RV+AGE cases were more likely to be classified as moderate or severe (69% among cases compared to 38% in group A controls (p<0.001; OR=3.57; IC 95%,1.82-7.04).

Social and demographic characteristics	Cases (57)	Control A Group (-104)		Control B Group (305)	
	N (%)	N (%)	p	N (%)	P
Age (months) (Median ± SD)	10 ± 6.30	15 ± 10.18	0.12	12 ± 9.78	0.36
Sex (male)	35 (61.4%)	69 (66.3%)	0.53	172 (56.4%)	0.66
Prematurity	4 (7.0%)	15 (14.4%)	0.16	41 (13.4%)	0.17
Breastfeeding	29 (50.9%)	46 (44.2%)	0.41	119 (39.0%)	0.09
Siblings	28 (49.1%)	45 (43.3%)	0.47	139 (45.6%)	0.62
Country of origin					
Spanish	48 (84.2%)	85 (81.8%)	-	273 (89.5%)	-
Foreign	9 (15.8%)	19 (18.2%)	0.69	32 (10.5%)	0.25

Table 1: Characteristics of the subjects.

Regarding vaccination status, five patients (8%) had received 1 or more doses of a rotavirus vaccine in the case group, forty-one (40%) in Control group A and 132 (43%) in Control group B. Vaccine effectiveness was estimated as 86% (95%CI 59-95) compared to Control group A and 88% (95%CI 68-95) compared to Control group B. (Figure 1).

Discussion

The effectiveness of rotavirus vaccines has been reported in numerous studies based on hospitals, emergencies departments and primary care settings, or using population-based surveillance methodology [16,17]. Our report represents the first case-control study matched by gender and age that analyses risk factors for rotavirus infection conducted in Spain, and contributes to assessing rotavirus vaccine effectiveness in Europe. Recently, several case-control studies carried out in Europe have been published, but few of them were matched by sex, age and timeframe of admission [18-21]. In our study, this matching has improved the comparability among the three groups with regard to risk factors for rotavirus disease. The case-control design we used, including two different matched control groups (non-rotavirus AGE and non-AGE hospitalized patients) provided comparison groups that were demographically similar to the matched cases, enhancing comparability. Since Control group B did not have AGE misclassification of cases and these controls was

unlikely. Other non-matched case-control studies that have investigated rotavirus vaccine effectiveness in Spain have been published recently [19-21]. In those studies, controls were older, less frequently hospitalized, and were seen in a different timeframe, making it necessary to use adjusted multiple logistic regression analyses. These factors have been incorporated in our matched study. Another issue to highlight is the high percentage of patients who had received at least one dose of vaccine among the control groups (40% and 43% respectively), compared with the low coverage found in other studies in Spain. Rotavirus vaccine uptake in Spain has been estimated using sales by region and this shows wide differences between them ranging from 6% to 63% (data unpublished, IMS Health). Such variance could be influenced by social and economic factors together with the knowledge, attitudes and practices of healthcare providers.
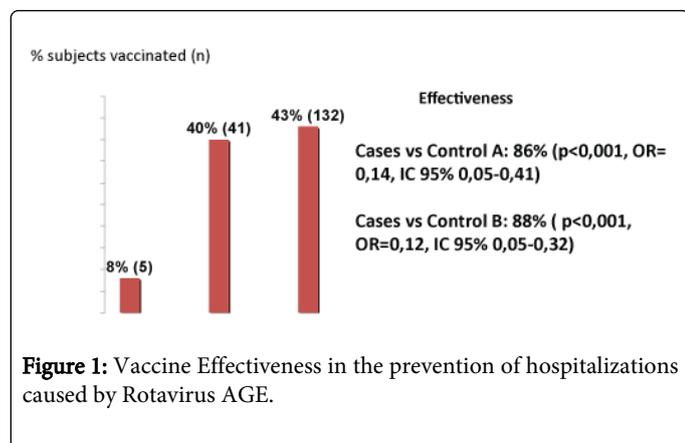

Figure 1: Vaccine Effectiveness in the prevention of hospitalizations caused by Rotavirus AGE.

Prior rotavirus vaccination was more frequent in mild cases than in those with moderate-severe symptoms (Figure 2). In addition, the average length of admission was shorter in vaccine recipients (1.7 ± 0.8 days) compared to those who had not been vaccinated (3.2 ± 1.4 days) ($p<0.001$; 95% CI: 1.3-1.7)
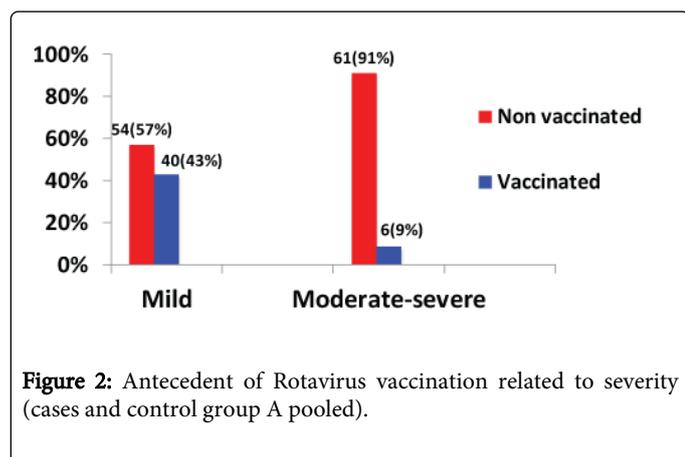

Figure 2: Antecedent of Rotavirus vaccination related to severity (cases and control group A pooled).

Our vaccine effectiveness estimates are similar to results found in other postmarketing case-control studies, showing a slightly lower effectiveness when compared with the results from randomized controlled trials [22-24]. However, Castilla et al. [20] and Bellido-Blasco et al (21) also using a case-control design in Spain, reported a vaccine effectiveness of 83% and 88% for hospitalized rotavirus cases among children aged <5 years and <3 years, respectively. This data is virtually identical to ours, although the study was from a different geographic region with a much lower vaccine uptake. Another study

conducted in Spain, including pooled patients who were hospitalized attended to in emergency departments and in the primary care system, with similar a rotavirus vaccine coverage to ours, found a vaccine effectiveness of 95% for the prevention of hospitalizations and 92% for any episode of AGE caused by rotavirus [19]. Additionally, these studies did not find differences in the effectiveness of the two brands of rotavirus vaccine marketed. With a similar methodology, another study in Israel showed a vaccine effectiveness of 89% using non-rotavirus AGE as controls [25]. Most studies conducted so far have found a lower level of protection when analysing cases of AGE in outpatient care, and a higher effectiveness in the prevention of cases of severe disease [26,27]. In our study, an important factor to take into account is that the Rate Ratios were analysed in hospitalized children and were not combined with outpatient cases, a fact that could give a better assessment of the risk of rotavirus infection. Recently, another matched case-control study, conducted in Belgium during the same time period as ours, found 90% vaccine effectiveness against rotavirus admissions. They considered children as vaccinated if they had received two doses of the monovalent rotavirus vaccine [18]. Data from developing countries with rotavirus vaccines have reported high effectiveness. A study in Nicaragua showed 83% vaccine effectiveness among children younger than 12 months, using a pentavalent vaccine, and a study from Brazil found a 76% using a monovalent vaccine [28-29]. Both these studies mentioned were matched case-control studies, and reported a lower effectiveness when cases were compared to hospitalized controls rather than those who were not hospitalized.

Our study found that rotavirus infected patients who had been vaccinated had a milder clinical presentation than the unvaccinated, which was similar to findings from another case control study conducted in Germany [30]. This could be explained by the likely capacity of rotavirus vaccines to confer partial protection, leading to less severe cases. Moreover, vaccinated subjects had a shorter length of admission compared with the unvaccinated, suggesting a faster recovery rate among them. It has been shown that the complete course of rotavirus vaccinations leads to a higher effectiveness compared to that among partially vaccinated children [19], but in our study the number of rotavirus vaccine administrated was not measured so this could not be correlated with the severity of disease, which could be considered a limitation of the study.

Our study has other limitations: the vaccine type was not analysed because this was not normally recorded in the immunization records by nurses. Thus, possible differences in effectiveness between the monovalent and pentavalent vaccines could not be measured. A potential bias could have been introduced because AGE cases might be misclassified if there are issues with the reliability of the rotavirus EIA results that could have led to a bias towards the null hypothesis. In our study, such misclassification should not have had a major impacted on our results, since the rotavirus EIA is reported to be >95% sensitive [31] and more than 95% of bulk stool specimens were collected within the first 48 hours. However, stool samples were not stored to be typed by molecular methods in future studies, which could be considered another shortcoming of the study. Finally, the number of rotavirus vaccine doses was not recorded so vaccine effectiveness based on the number of doses received could not be calculated. Thus, a bias towards the null (lower vaccine effectiveness) could have derived from the misclassification of children vaccinated with just one dose among those vaccinated with more than one dose.

In conclusion, our study found rotavirus vaccines to be highly effective in preventing rotavirus-related hospitalizations. The

effectiveness we found was similar to that obtained in studies from other European regions some of which used different methodologies. In addition, a reduction in the length of hospital stays due to rotavirus infection was observed among vaccinated cases, suggesting effectiveness also against the disease's severity. Our results should be useful to establish future recommendations for rotavirus vaccination.

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