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Original article

Effectiveness of rotavirus pentavalent vaccine under a universal immunization programme in Israel, 2011–2015: a case–control study

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ABSTRACT

Objectives: The use of rotavirus pentavalent vaccine (RotaTeq®) as a sole vaccine within rotavirus universal immunization programmes remains limited. We examined the effectiveness of RotaTeq in preventing rotavirus gastroenteritis (RVGE) hospitalization in Israel, after the introduction of universal immunization against the disease.

Methods: A test-negative case–control study included age-eligible children for universal RotaTeq immunization (aged 2–59 months, born in 2011–2015). Cases ($n = 98$) were patients who tested positive for rotavirus by immunochromatography; those who tested negative ($n = 628$) comprised the control group. Information on rotavirus immunization history was obtained through linkage with a national immunization registry. Vaccination status was compared between cases and controls, adjusted odds ratios (aORs) were obtained from logistic regression models, and vaccine effectiveness calculated as $(1 - \text{aOR})^*100$.

Results: Immunization with RotaTeq was less frequent in RVGE cases (73.5%) than in controls (90.1%), $p < 0.001$; this association persisted after controlling for potential confounders. Effectiveness of the complete vaccine series was estimated at 77% (95% confidence interval (CI): 49–90) in children aged 6–59 months, and 86% (95% CI: 65–94) in children aged 6–23 months; whereas for the incomplete series, the respective estimates were 72% (95% CI: 28–89) and 75% (95% CI: 30–91). Vaccine effectiveness was estimated at 79% (95% CI: 45–92) against G1P[8]-associated RVGE hospitalizations and 69% (95% CI: 11–89) against other genotype-RVGE hospitalizations.

Conclusions: High effectiveness of RotaTeq as the sole rotavirus vaccine in a universal immunization programme was demonstrated in a high-income country. Although partial vaccination conferred protection, completing the vaccine series is warranted to maximize the benefit. **K. Muhsen, Clin Microbiol Infect 2018;24:53**

Introduction

Rotavirus is the main cause of severe diarrhoea in children [1] and a leading cause of child mortality in developing countries [2]. Two rotavirus vaccines became available globally in recent years, both administered orally [3,4]. One is a monovalent vaccine containing attenuated human G1P[8] rotavirus strain (Rotarix®, GlaxoSmithKline Biologicals, Brentford, UK), administered in two doses

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at ages 2 and 4 months [4]. The other is a pentavalent live bovine–human reassortant vaccine (RotaTeq®, Merck and Co., Inc., Whitehouse Station, NJ, USA) containing strains representing G1, G2, G3, G4 and P[8] genotypes, and administered in three doses, at ages 2, 4 and 6 months [3]. Although different disease severity scoring systems were used, both vaccines showed high efficacy (85–95%) in preventing severe rotavirus gastroenteritis (RVGE) in clinical trials conducted in Europe and the Americas [3,4]. Rotavirus vaccine efficacy was low (40–61%) in developing countries [5].

The World Health Organization (WHO) recommends including rotavirus vaccine in national immunization programmes worldwide [6]. By September 2016, a decade after rotavirus vaccines became available, 81 countries had introduced rotavirus immunization into national immunization programmes and seven countries had introduced rotavirus immunization in certain regions only [7]. Presently, most countries use Rotarix [7].

Significant and sustained reduction in the burden of RVGE was observed in countries that introduced rotavirus immunization, including Israel [8–14]. These studies employed mostly ecological design, comparing the incidence of RVGE in the entire target population, both vaccinated and unvaccinated groups, before and after the introduction of universal rotavirus immunization. The impact of universal rotavirus immunization on disease burden in the population is a function of vaccine coverage, vaccine effectiveness and possibly herd immunity. Numerous postmarking evaluations have assessed rotavirus vaccine effectiveness, mostly using a test-negative case–control study design [15–19]. In this efficient and cost-saving design, rotavirus immunization history is compared between RVGE cases and control diarrhoea patients who test negative for rotavirus [20]. Due to the limited introduction of rotavirus vaccines in high-income countries, and since most of them introduced Rotarix, updated evidence of the net effectiveness of RotaTeq as a sole vaccine under universal vaccination policy in high-income settings, outside the USA, remains scarce [17,21].

In Israel, both rotavirus vaccines were licensed and became available by the end of 2007 in the private market, with partial refund through the health maintenance organizations. In December 2010, RotaTeq was introduced in the national immunization programme, free of charge for all children, and since that time it has been the only vaccine used.

An Israeli study that comprised 70% Bedouin children reported 63% vaccine effectiveness for RotaTeq [21]. Bedouins are a small sub-group of the Arab minority in Israel, and typically live in low socioeconomic and suboptimal environmental conditions, thus generalizability from that study remains limited. We examined the effectiveness of RotaTeq in a universal immunization programme, in preventing RVGE hospitalization during 2011–2015 in Israel, as a model of a high-income country.

Methods

Study population and design

A hospital-based active surveillance study was conducted between November 2007 and February 2016 in northern Israel, following a generic protocol of the WHO [22]. Details of the study design have been published elsewhere [13,14,23,24]. The study included children 0–59 months of age residing in the catchment area of three hospitals: Hillel Yaffe in Hadera, Carmel in Haifa, and Laniado in Netanya. Both Jewish and Arab residents live in the study area.

According to the Universal National Health Insurance Law, all Israelis have access to medical care. The national immunization programme is conducted at maternal and child health clinics. RotaTeq is administered at ages 2, 4 and 6 months; the estimated vaccine coverage is >80%.

The sampling frame included children who were hospitalized due to diarrhoea (three or more watery stools during a 24 h period) [13,14,23–25]. During the study period, research staff in each hospital were instructed to systematically collect stool samples from all children hospitalized for diarrhoea and to submit the samples for rotavirus antigen testing at the local laboratory in each hospital.

The current test-negative case–control study was restricted to birth cohorts of the years 2011–2015 who were eligible for RotaTeq under universal immunization and hospitalized during 2011–2015. We set a lowest age limit at admission as 2 months, since this is the recommended age for the first RotaTeq dose. Children who were not tested for rotavirus or without information on rotavirus immunization were excluded from the analysis.

Parents were interviewed concerning demographic and clinical information on the number of stools passed, vomiting and fever. Information on rotavirus vaccination history was obtained through linkage with the national immunization registry at the Ministry of Health.

If parents expressed refusal to vaccinate their child, that information would be documented in the child's medical record, and was collected through the linkage with the immunization registry. Information on immunization was collected for children hospitalized until October 2015.

Vaccination status was determined up to the admission date. Children were classified as unvaccinated or vaccinated with at least one dose, and according to the number of doses.

Socioeconomic status (SES) was classified on a scale of 1–10, according to the socioeconomic rank of the town of residence, as defined by the Israel Central Bureau of Statistics [26]. The ranks were grouped into three categories of SES: 1–3 (low), 4–5 (intermediate) and 6–10 (high).

Laboratory methods

Stool samples were collected from patients within the first 48 h of hospitalization. Specimens were tested for rotavirus antigen by immunochromatography (Rotavirus Dipsticks, Hylabs Rehovot & Novamed, Jerusalem, Israel), according to manufacturers' instructions. In practice, 87% of the analysed stools were tested within 2 days of admission, 95% within 3 days. Cases were children with a confirmed rotavirus-positive test in their stool, and controls were patients who tested negative for rotavirus.

After performing the rotavirus test, the remaining faecal material was transferred to the Central Virology Laboratory in cool conditions. Specimens were kept at −70°C until genotyping was performed [14].

Statistical methods

χ^2-Test and Fisher's exact test, as appropriate, were used to examine differences between vaccinated and unvaccinated children in sociodemographic characteristics, season/year of admission and birth year. Similarly, differences between RVGE cases and test-negative controls were examined. Logistic regression models were fitted to obtain adjusted odds ratio (aOR) and 95% confidence interval (CI) for immunization status before admission. The models were adjusted for vaccination status, age, year and season of admission and SES. Vaccine effectiveness was calculated as (1 − aOR), and expressed as a percentage [27].

The primary analyses were limited to children 6–59 months of age, assuming that those children were all eligible for the full vaccine series. Additional analyses were performed with