Vaccine 33 (2015) 1934–1940

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Rapid impact of rotavirus vaccine introduction to the National Immunization Plan in Southern Israel: Comparison between 2 distinct populations

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ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form 19 February 2015
Accepted 23 February 2015
Available online 3 March 2015

Keywords:
Rotavirus
Rotavirus vaccine
Gastroenteritis

ABSTRACT

Background: Rotavirus vaccines were licensed in Israel in 2007, and in 2011 the pentavalent-vaccine (RV5) was introduced into the Israeli National Immunization plan.
Aim: To determine the effect of rotavirus-vaccines on the incidence of hospital visits due to rotavirus gastroenteritis (RVGE) and all-cause diarrhea in Jewish and Bedouin children <5 year residing in southern Israel.
Methods: We conducted a population-based, prospective, observational study. Data from 2006 through 2013 were analyzed. Our hospital is the only medical center in the region, enabling age-specific incidences calculation.
Results: In the pre-vaccine period, the overall RVGE hospital visits rates per 1000 in children <12, 12–23 and 24–59 m were 16.1, 18.6 and 1.4 in Jewish children, respectively. The respective rates in Bedouin children were 26.4, 12.5 and 0.7 ($P<0.001$ for <12 m).

Hospitalization rates were higher among Bedouin than among Jewish children (60.0% *vs.* 39.7%, $P<0.001$). Vaccine uptake was faster in the Jewish *vs.* the Bedouin population.

In the year following RV5 introduction, RVGE hospital visits rates declined by 82%, 70% ($P<0.001$ both) and 36% ($P=0.092$) in Jewish children <12, 12–23 and 24–59 m, respectively. In Bedouin children, the respective RVGE rates declined by 70% ($P<0.001$), 21% ($P=$ ns) and 14% ($P=$ ns).

Throughout the study, RVGE rates declined significantly in children <12, and 12–23 m by 80% and 88% in Jewish children, respectively, and by 62 and 75% in Bedouin children, respectively ($P<0.001$ for all declines). In children 24–59 m, RVGE rates declined by 46% ($P=0.025$) in Jewish children, but no reduction was observed in Bedouin children. The dynamics of all-cause diarrhea rates were similar to that of RVGE.
Conclusions: Significant reductions of RVGE rates were observed, following Rota-vaccine introduction in southern Israel in both Jewish and Bedouin children. However, the impact was faster and more profound in Jewish children, probably related to higher vaccine uptake and possibly to lifestyle differences.

1. Introduction

Rotavirus is the leading cause of severe diarrhea in infants and young children globally [1,2]. Two live highly efficacious oral rotavirus vaccines are currently licensed: A monovalent vaccine (Rotarix™; RV1) and a pentavalent vaccine (Rotateq™; RV5). Introducing either vaccine to National Immunization Programs (NIPs) resulted in a rapid and profound reduction in rotavirus burden [3–8]. Furthermore, an indirect protection in unvaccinated contacts (herd protection) was also described [9,10]. Rotavirus vaccines are now licensed in >100 countries, and have been included in the NIPs of ~50 countries [11], including several European countries [12].

Studies on rotavirus disease burden in Israel showed similar findings to that from other developed populations [13,14]. In southern Israel (the Negev region), Jewish and Bedouin populations

Abbreviations: RV5, pentavalent vaccine (Rotateq™); RVGE, rotavirus gastroenteritis; RV1, monovalent vaccine (Rotarix™); NIP, National Immunization Program; PER, pediatric emergency room; LRI, lower respiratory infection; URI, upper respiratory infection; GE, gastroenteritis.

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http://dx.doi.org/10.1016/j.vaccine.2015.02.062
0264-410X/

live side by side, but differ in socioeconomic conditions, lifestyle, and health-seeking behavior; the Jewish population resembles a developed population, and the Bedouin population has common characteristics with developing populations [15]. Over 95% of children in southern Israel are born in a single hospital, where they also receive all hospital medical services (from the only Pediatric Emergency Room [PER] in the region), enabling population-based studies.

Both rotavirus vaccines were licensed in Israel in 2007 but were initially only scarcely used. From mid-2008 to December 2010, they have been distributed at reduced costs by the health maintenance organizations, covering ~25% of the Jewish children with ≥1 doses. In contrast, the Bedouin population did not use any rotavirus vaccine during that period (data source: Pediatric Infectious Disease Unit, Beer-Sheva, Israel). In January 2011, RV5 was introduced into the Israeli NIP, and offered free of charge to all infants born after September 1st 2010; it was administered at ages 2, 4 and 6 months.

Anticipating rotavirus vaccine introduction, we initiated a population-based prospective study in April 2006 to characterize rotavirus gastroenteritis (RVGE) dynamics before and after the introduction of rotavirus vaccines with four objectives: (1) To determine of rotavirus vaccines effect on the incidence of PER visits and hospitalization due to RVGE and all-cause diarrhea; (2) to compare RVGE rate dynamics to that of non-rotavirus gastroenteritis and respiratory infections; (3) to compare RVGE burden and rotavirus vaccination impact between Jewish and Bedouin children; and (4) to assess the potential indirect effect of infant vaccination on older children <5 years of age (2–4 years of age).

2. Materials and methods

2.1. Study design and conduct

This was a prospective hospital-based, population-based observational study conducted during a 7-year period (April 2006–March 2013). The fact that the study was conducted in the only medical center in the region, which treats essentially all patients in the area (>95% case capture) with a defined birth cohort, enabled age-specific incidence calculation. Population numbers were drawn from the Central Bureau of Statistics, for appropriate years, ages and ethnicity [16]. During the first study years, the <2 and <5 years populations of southern Israel were ~30,000 and ~72,000 children, respectively. The respective populations for the entire country were ~300,000 and ~730,000 children.

The study was approved by the Soroka University Medical Center and the Ministry of Health's Ethics Committees.

Study staff located at the PER identified all eligible children daily, year round (including weekend and holidays) from 8:00 AM to 9:00 PM. All children <5 years with a history of diarrhea/vomiting (≥3 watery or looser-than normal stool within a 24 h period and/or forceful vomiting) were offered participation upon presentation to the PER and parental consent was sought. A standardized questionnaire was administered by the study staff and a bulk stool specimen was obtained. Demographic data (ethnic group, age, gender), duration of hospitalization and rotavirus vaccination status were recorded. Inpatients were defined as subjects who were admitted to the hospital for ≥24 h.

A stool sample was collected from the diaper or directly from the child within 48 h of admission. If the stool sample was soaked into the lining of the diaper, an 11 cm^2 stool-impregnated piece was cut from the internal section of the diaper. The study was interrupted, and no subjects were enrolled, during April through October 2009 (which are outside the rotavirus season), due to budget constraints, but resumed with identical design to the initial phase, in November 2009.

All study cases were of hospital-visits in the PER, with patients discharged from the PER regarded as "outpatients" and hospitalized patients regarded as 'inpatients".

We divided the study years into 4 periods: *First period* (pre-vaccine): April 2006 through March 2008 when none of the children in southern Israel used any of the rotavirus vaccine; *second period* (limited vaccine use): April 2008 through March 2011, when ~25% of the Jewish children received ≥1 doses of either RV1 or RV5 (purchased privately), whereas Bedouin children did not receive any rotavirus vaccine; *third period* (first post-NIP year): April 2011 through March 2012, the first year following RV5 introduction to the NIP; and *fourth period* (second post-NIP year): April 2012 through March 2013, the second year following RV5 introduction.

Rota season was defined as the period between November and March.

2.2. Case definition

A case needed to fulfill all of the following: (1) age <5 years; (2) residing in the Negev region; (3) presenting with an episode of ≥3 watery or looser-than-normal stools within a 24 h period and/or forceful vomiting (excluding post-tussive vomiting); (4) the current diarrhea episode started within the past 6 days and; (5) a stool or diaper specimen was collected from the subject.

Two scales, the Vesikari 20-point scale, and the Clark 24-point scale, were used to evaluate RVGE cases severity [15].

As background information, we collected all PER visits and hospitalizations of children <5 years caused by lower respiratory infection (LRI), upper respiratory infection (URI) and gastroenteritis (GE). These were recorded daily (data derived from ICD-9 diagnoses).

2.3. Laboratory methods

All samples were sent to the Pediatric Infectious Disease Unit Research Laboratory, where a 20% stool suspension in Earle's balanced salt solution (EBSS)+ Ca^{++} was made and stored at −70 °C. The presence of rotavirus antigen (VP6) was detected using the IDEIA™ rotavirus ELISA kit (DakoCytomation Ltd., Cambridgeshire, UK).

2.4. Vaccine uptake

Vaccine uptake was calculated from 2 sources: The first source was a prospective study on vaccination rate in southern Israel, initiated in 2009 [17]. Briefly, in each working day, the first 4 Jewish and 4 Moslem-Bedouin children, seen at the Soroka University Medical Center's PER for any reason, were enrolled in the vaccine uptake study. For each child, the vaccination status and dates of administration were recorded. The return rate was >95%. The second source for vaccine status was calculated in children enrolled in the study who had rotavirus-negative diarrhea. The 2 sources were grouped and duplicates were excluded.

We examined vaccine uptake in children 8–11 months old, since the upper limit age for rotavirus vaccination in Israel is 7 months, and we wanted to include children in their first year of life.

2.5. Statistical methods

Incidences, disease burden and relative burden of RVGE *vs.* other major diseases (LRI, URI and GE) were calculated separately for the 4 above mentioned study periods. Incidences were calculated annually (April through March, each year) as the number of RVGE cases divided by the total population at risk during each year of the study. The ethnicity-specific populations at risk were estimated according to the Israeli Central Bureau of Statistics reports for the appropriate years [16].