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Decline of rotavirus-coded hospitalizations in children under 5 years: A report from Japan where rotavirus vaccines are self-financed

Masayuki Kobayashi [a,*], Noriaki Adachi [b], Makoto Miyazaki [c], Masatoshi Tatsumi [d]

[a] Medical Affairs, MSD K.K., Tokyo, Japan
[b] Biostatistics and Research Decision Sciences, MSD K.K., Tokyo, Japan
[c] Risk Assessment & Pharmacoepidemiology, MSD K.K., Tokyo, Japan
[d] Department of Pediatrics, Otaru Kyokai Hospital, Otaru City, Japan

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ABSTRACT

Objectives: To estimate the trend in incidence of rotavirus gastroenteritis (RVGE) hospitalization among children aged <5 years in Japan during pre- and post-vaccine periods (2009–2011 and 2012–2015).
Study design: This retrospective observational study used a health insurance claims database (constructed by Japan Medical Data Center Co., Ltd.). Rotavirus vaccine became commercially available in 2011. We analyzed data of all children aged <5 years between January 2009 and December 2015. We estimated the incidence rate (IR) of RVGE hospitalization per 1000 person-years from 2009 to 2015 and incidence rate ratio (IRR) of post-vaccine years compared with the averaged pre-vaccine years. IRs and IRRs were also estimated by age group. Primary analysis was limited to the rotavirus season (January to June) of each year.
Results: The IR was 6.3–9.3 in pre-vaccine years, 2.3 in 2014, and 3.0 in 2015; the decline was estimated to be 71% in 2014 and 61% in 2015 ($p < 0.01$). By age group, reduction in hospitalizations began in 2013 among children <1 year old, followed by children aged 1 to <5 years in 2014. In the 2014 season, a 65% reduction in RVGE hospitalization was observed in children aged 36 to <60 months, although this age group was unlikely to be vaccinated.
Conclusions: A substantial decline of RVGE hospitalization in 2014 and its persistence was observed among children aged <5 years in Japan after introduction of rotavirus vaccine, although not included in the national immunization program. Indirect effects of rotavirus vaccination were suggested in the 2014 season.

1. Introduction

Rotavirus (RV) is the leading cause of acute severe childhood gastroenteritis. The prominent feature of rotavirus gastroenteritis (RVGE) is watery diarrhea with vomiting and fever [1,2]. Nearly all children aged <5 years are infected with RV at least once, regardless of socioeconomic status or environmental conditions [3]. Estimated deaths caused by RV among children aged <5 years worldwide, particularly those in developing countries, were 528,000 in 2000 and 215,000 in 2013 [4]. After first being introduced in 2006, RV vaccines have been included in the national immunization programs of 86 countries, as of September 2016 [5].

The two-dose monovalent RV1 (Rotarix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) and three-dose pentavalent RV5 (RotaTeq®, Merck & Co., Inc., Kenilworth, NJ, USA) rotavirus vaccines became available in Japan in November 2011 and July 2012, respectively. Introduction of RV vaccines into the routine national immunization program has been under discussion but has not yet occurred. Although not included in the routine national immunization program, the estimated national coverage of RV vaccination in Japan after the introduction of RV vaccines increased from 32% in 2012 to around 60% in 2014 [6]. Further increases can be expected in subsequent seasons.

Though fatal cases caused by RVGE are rare in Japan, previous municipality-based studies conducted during pre-vaccine years have estimated that over 790,000 children aged <6 years presented

Abbreviations: AGE, acute gastroenteritis; CI, confidence interval; IASR, Infectious Agent Surveillance Report; IR, incidence rate; IRR, incidence rate ratio; mo, month; Ref, reference category; RV, rotavirus; RVGE, rotavirus gastroenteritis.

* Corresponding author.
E-mail address: masayuki.kobayashi@merck.com (M. Kobayashi).

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to hospitals or clinics as outpatients each year owing to RVGE [7], and that approximately 78,000 children aged <5 years were hospitalized annually because of RV-related disease [8]. However, information is limited on the incidence trend of RVGE over time, during the periods before and after RV vaccines became available in Japan.

The present study aimed to estimate and describe the trend in incidence of severe RVGE (requiring hospitalization) among children aged <5 years in Japan during the RV seasons in pre- and post-vaccine years, from 2009 to 2015.

2. Patients and methods

2.1. Study design and data source

The present study was a retrospective, observational, database study adopting an ecological design. The data source was an employment-based health insurance claims database constructed by Japan Medical Data Center Co. Ltd. (JMDC; Tokyo, Japan). The database includes claims and enrollment data of approximately 2.8 million corporate employees and their families from over 50 health insurance associations in 2015; these data accounted for 2.3% of the total Japanese population. More than 200,000 children aged <5 years were included in 2015, accounting for about 4.0% of children in that age group in Japan. Nearly all medical services provided by medical institutions are covered by health insurance that is either employment-based, municipality-based, or a separate system for individuals aged ≥75 years. The database used contains nearly the entire medical history of each individual and their family members covered by employment-based health insurance, even if they attend multiple medical institutions, unless the individual withdraws from the health insurance. However, no data of RV vaccination history are available in the dataset as vaccination is supported by municipalities in Japan and is not covered by health insurance. We extracted inpatient claims data from the database for the present study.

As this study used existing data that were de-identified, obtaining patient informed consent was not required. The protocol of the present study was reviewed and approved by the ethics committee of the Japan Epidemiological Association (Approval number: 16003). This study was registered in the University Hospital Medical Information Network (UMIN), Japan (ID: UMIN000024647).

2.2. Inclusion and exclusion criteria

All children who were aged <5 years during the study period (January 1, 2009, to December 31, 2015) were included in the analysis. No exclusion criteria were applied. The follow-up period ended on December 31, 2015, unless a child reached age 5 years or withdrew from health insurance during the study period.

2.3. Outcome

Our primary outcome was hospitalization because of RVGE, defined as hospitalization with a newly assigned diagnosis code of A08.0, rotaviral enteritis, according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). If a child had multiple RVGE hospitalizations in consecutive months, these events were treated as a single event. Otherwise, repeat hospitalizations were treated as independent events. Our secondary outcome was hospitalization because of AGE, defined as inpatient hospitalization with any of the following newly assigned ICD-10 diagnosis codes: A08.0, rotaviral enteritis; A08.1, acute gastroenteropathy due to Norwalk agent; A08.2, adenoviral enteritis; A08.3, other viral enteritis; A08.4, viral intestinal infection, unspecified; A08.5, other specified intestinal infections; A09.0, other and unspecified gastroenteritis and colitis of infectious origin; or A09.9, gastroenteritis and colitis of unspecified origin. Multiple AGE hospitalizations were treated in the same manner as multiple RVGE hospitalizations. Each diagnosis in the claims database is recorded as either fixed or suspected diagnosis. In this study, we only used hospitalizations with a fixed diagnosis.

2.4. Statistical analysis

To obtain the trend of RVGE hospitalization from 2009 to 2015, the incidence rate (IR) per 1000 person-years was estimated for each season, after obtaining the total number of children and person-years. For the calculation of person-years, all children were assumed to be born on the 1st day of their birth month because only year and month of birth are available in the database.

For a comparison of RVGE hospitalizations between the pre- and post-vaccine periods, the incidence rate ratio (IRR) was estimated. We defined the pre-vaccine period as 2009–2011 because the first RV vaccine became available in November 2011; the post-vaccine period was defined as 2012–2015. The IRR against the averaged IR of the pre-vaccine period was computed for each post-vaccine season (2012–2015), using a Poisson regression model, controlling for age and sex as potential confounders. Our primary analysis was limited to the RV season; this is defined as from January to June of each year, as the number of detected RV agents increases from January and decreases after June according to the national Infectious Agent Surveillance Reports (IASRs) [9]. We conducted the identical analysis for the secondary outcome of AGE and analysis for the entire year.

Subsequently, we further analyzed IR and IRR for RVGE, stratified by the following five age groups, for each RV season: <6 months, 6 to <12 months, 12 to <24 months, 24 to <36 months, and 36 to <60 months of age, without adjustments. All statistical tests were two-sided with a significance level of 0.05, and were carried out using SAS release 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

Between 2009 and 2011, the IR of RVGE ranged from 6.3 to 9.3 per 1000 person-years. As shown in Fig. 1A, a sharp decrease in the IR was observed after the 2014 season (2.3 in 2014 and 3.0 in 2015), with a moderate increase in the estimated national RV vaccine coverage (i.e., 32% in July 2012, 51% in April 2013, and around 60% in May 2014) [6]. Similarly, the IR for AGE in the RV season steadily declined during the post-vaccine period, particularly in 2014 and 2015 (13.6 and 14.2, respectively, compared with 21.6–23.8 in the pre-vaccine period), shown in Fig. 1B.

The IRR of RVGE hospitalizations in the RV season during the post-vaccine period compared with the pre-vaccine average is shown in Table 1 (entire-year data are presented in Supplementary File 1). RVGE hospitalizations dropped significantly by 71% in 2014 and 61% in 2015 season, respectively, compared with the pre-vaccine period (nominal p-value < 0.01). As the results were identical with and without adjustment for age and sex, Table 1 and Supplementary File 1 show only adjusted results.

The IR and IRR for RVGE hospitalizations in the RV season, stratified by age group, are shown in Fig. 2. The IR for RVGE hospitalization was the highest during the pre- and post-vaccine periods for the age group 12 to <24 months, ranging from 17.4 per 1000 person-years in 2011 (data not shown) to 3.6 per 1000 person-years in 2014. This was followed by the neighboring age groups (6 to <12 months and 24 to <36 months) and then children aged <6 months and 36 to <60 months. A drastic decline in IRs of RVGE hospitalization compared with pre-vaccine years was seen in the 2013 season among the age groups <6 months and 6 to <12 mont

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