

RESEARCH PAPER



Sustained reduction in rotavirus-coded hospitalizations in children aged <5 years after introduction of self-financed rotavirus vaccines in Japan

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ABSTRACT

This is an extension of our previous study, which evaluated the incidence of seasonal rotavirus gastroenteritis (RVGE) hospitalizations in children aged <5 years from 2009 to 2015 in Japan. Here, we evaluated the incidence of RVGE hospitalizations in children aged <10 years during the rotavirus season (January–June) from 2009 to 2017 in Japan, before and after the monovalent and pentavalent rotavirus vaccines were introduced in November 2011 and July 2012, using the same health insurance claims database and study methods. In children aged <5 years, the incidence of RVGE hospitalizations greatly declined in 2014 after vaccine introduction, consistent with our previous findings, and the decline was sustained until 2017. However, in children aged ≥5–<10 years, no apparent trend for a continuous decline in RVGE hospitalizations was observed during the study period. Improved RV vaccination coverage may lead to a further reduction in severe RVGE in Japan.

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Introduction

Almost all children are infected with rotavirus (RV) by the age of five, regardless of sanitation standards, their socioeconomic status, and hygiene.¹ In the early 2000s, in Japan, 790,000 children aged <6 years visited healthcare institutions, and 78,000 children aged <5 were hospitalized for rotavirus gastroenteritis (RVGE).^{2,3} A decade later, RVGE incidences remained high (255 per 1000 person-years in children aged <3 years).⁴

To date, two oral RV vaccines, namely RotaTeqTM (Merck & Co., Inc., Kenilworth NJ, USA) and RotarixTM (GlaxoSmithKline Biologicals, Rixensart, Belgium), have been approved in over 120 countries. These vaccines are included in the national immunization programs of nearly 100 countries.⁵ In Japan, RotarixTM and RotaTeqTM became available in November 2011 and July 2012, respectively, through self-finance, and coverage of these vaccines increased to over 70% in 2017.⁶ The introduction of these vaccines into the routine national immunization program is under discussion at the Ministry of Health, Labour and Welfare of Japan.

So far, a few municipality-level studies have evaluated the impact of RV vaccine on the health of children aged <5 years in Japan.^{7–9} However, the results do not necessarily indicate a national trend. Hence, our previous study estimated the impact of RV vaccine on RVGE incidences in a large population of children aged <5 during the pre- and post-vaccination periods from 2009 to 2015 using a health insurance claims database.¹⁰ The results showed that there was a substantial decline in the incidence of RVGE-coded hospitalizations in the 2014 and 2015 seasons. However, data on the long-term impact of RV vaccines

are quite limited, especially for a large population in Japan. Additionally, its effect on older children is yet to be studied.

Hence, in this study, the objective was to evaluate the incidence of severe RVGE (hospitalizations due to RVGE) during the RV season (January–June) from 2009 to 2017 in children aged <10 years in Japan, before and after the introduction of the RV vaccines, using the same health insurance claims database as in our earlier study.¹⁰

Methods

Study design and data source

This was a retrospective, observational, database study, adopting an ecological design. This is an extension and expansion of our previous study¹⁰ using the same database, constructed by JMDC Inc. (Tokyo, Japan), based on employment-based health insurance claims from corporate employees and their dependents. The detailed methods used were previously reported.¹⁰ Some changes have been made to the database since our previous study: data from some newly contracted health insurance associations have been added after the previous study to the database, and data from dissolved associations or from associations whose contracts have been terminated have been withdrawn. Over 490,000 children in the database were aged <10 years in 2017, and over 240,000 children were aged <5 (each representing 5.0% of the children in these age groups in Japan). The study protocol was approved by the ethical committee of the Research Institute of Health Data

Science (RI2018007) and the study was registered as UMIN000033033.

Inclusion and exclusion criteria

All children who were <10 years of age during the study period (1st January 2009 to 31st December 2017) were included in the analysis. No exclusion criteria were applied. The follow-up period ended on 31st December 2017, unless a child reached 10 years of age or was withdrawn from the health insurance association during the study period.

Outcome

The primary outcome parameter was hospitalization due to RVGE, defined as hospitalization with a new fixed disease code of A08.0, rotaviral enteritis, according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Hospitalization due to acute gastroenteritis (AGE) was identified as a secondary outcome and was defined as hospitalization with a new fixed diagnosis of any of the following ICD-10 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 RVGE or AGE hospitalizations over consecutive months were considered as a single event because claims for the treatment are processed on a monthly basis and it is impossible to distinguish identical events.

Statistical analysis

Monthly incidence proportions of RVGE hospitalizations from 2009 to 2017 in each of the <5 and ≥ 5 –<10 years age

groups were calculated by dividing the number of events by the total number of children in each age group.

To assess the trends in RVGE hospitalizations from 2009 to 2017 in age groups of <5 years and ≥ 5 –<10 years, the incidence rate (IR) per 1000 person-years and the corresponding 95% confidence interval (CI) were estimated. To compare RVGE hospitalizations in the pre- and post-vaccine periods, 2009 to 2011 and 2012 to 2017, respectively, of children in both age groups, the incidence rate ratio (IRR) was estimated. The IRR against the averaged IR of the pre-vaccine period was calculated for each post-vaccine year using a Poisson regression model. The IRR was adjusted for age and gender as potential confounding factors in children aged <5. The IR and IRR for AGE hospitalizations were analyzed in the same manner.

We further analyzed the IR and IRR for RVGE hospitalizations stratified by finer age groups for children aged <5 years, as the number of events was sufficient in this age group. Although the same analysis was attempted for the finer age groups for children aged ≥ 5 –<10 years, the number of events was not considered to be sufficient. Our analyses of IR and IRR were limited to the RV season (January–June of each year), because the number of detected RV agents increases from January and decreases after June.¹¹

For all analyses, two-sided tests were performed with the level of significance set at $p < .05$, using SAS release 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Figure 1 shows the overall trend in the monthly incidence proportion of RVGE hospitalizations from 2009 to 2017. The highest proportions of RVGE hospitalizations were observed during March and April of each year. Figure 1 also shows that there was a higher incidence of RVGE hospitalizations in children aged <5 years than in children aged ≥ 5 –<10 throughout the study period. However, the incidence of RVGE

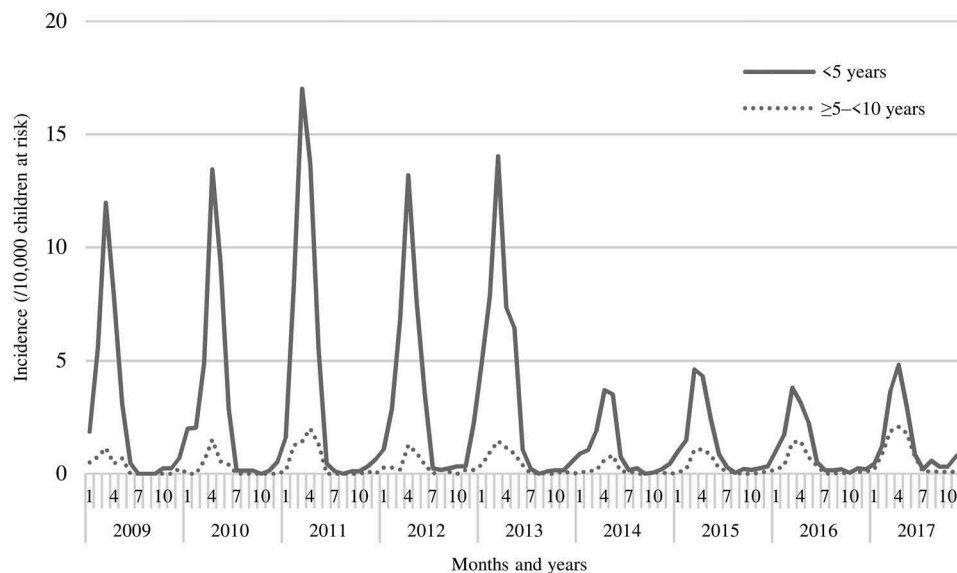


Figure 1. Monthly incidence proportions of RVGE hospitalizations from 2009 to 2017 in the <5 and ≥ 5 –<10 years age groups. RVGE: rotavirus gastroenteritis.

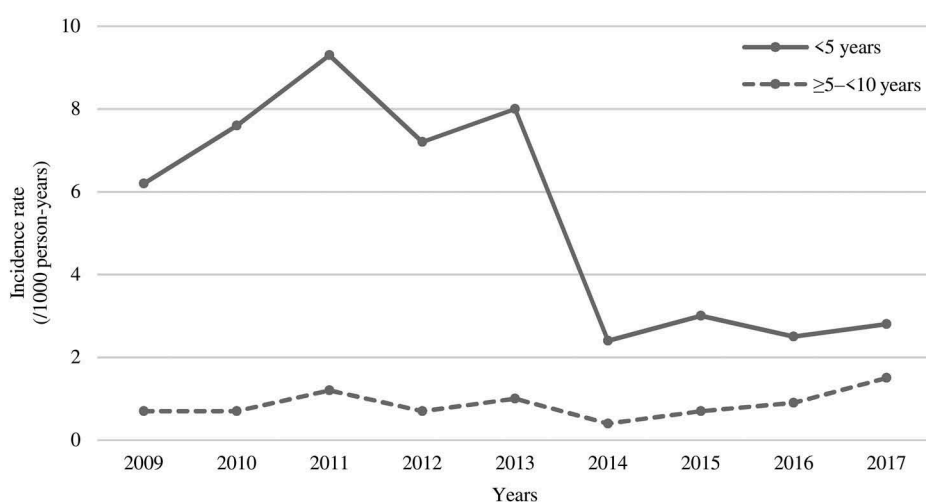
hospitalizations in children aged <5 sharply declined in 2014 and this decline was sustained thereafter.

In children aged <5 years, the IR (95% CI) of RVGE hospitalizations ranged from 6.2 (5.2–7.4) to 9.3 (8.4–10.3) per 1000 person-years from 2009 to 2013 (Figure 2). A sharp decline of 69% in the incidence of RVGE hospitalizations was observed in 2014 compared to that in the pre-vaccine period (nominal $p < 0.001$) (Table 1), to an IR of 2.4 (2.1–2.7) per 1000 person-years (Figure 2). After 2014, the IR of RVGE hospitalizations remained significantly lower until 2017, the end of the study. However, in children aged ≥ 5 –<10, no substantial variation was observed in the incidence of RVGE hospitalizations (0.4–1.5 per 1000 person-years) throughout the study period. The IR and IRR for AGE hospitalizations followed a similar pattern to the data for RVGE (Supplementary Figure 1 and Supplementary Table 1).

When the results for children aged <5 years were stratified by age group (Figure 3), we observed that the incidence of RVGE hospitalizations substantially decreased in 2013 by 33% in children aged <6 months and by 49% in children aged ≥ 6 –<12 months compared to that in the pre-vaccine period. Thereafter, the incidence remained low throughout the study. In the rest of the groups (≥ 12 –<24 months, ≥ 24 –<36 months, and ≥ 36 –<60 months), a large drop of 62%–75% in the incidence of RVGE hospitalizations was observed in 2014 compared to that in the pre-vaccine period (nominal $p < .001$), and this lower incidence was sustained.

Discussion

The results of this extended study, which indicate that there was a decline in the rotavirus-coded hospitalizations in children aged <5 years during the 2014 and 2015 seasons, are



Age group	2009	2010	2011	2012	2013	2014	2015	2016	2017
<5 years									
n	46829	78501	100029	130905	201355	218787	264126	274557	273383
Person-years	20290	30187	43193	58003	79673	97858	111275	123346	124405
IR	6.2	7.6	9.3	7.2	8.0	2.4	3.0	2.5	2.8
95% CI	5.2–7.4	6.7–8.7	8.4–10.3	6.5–7.9	7.4–8.7	2.1–2.7	2.7–3.3	2.2–2.8	2.5–3.1
≥ 5 –<10 years									
n	48799	78791	99131	129135	195879	213957	259664	274113	274317
Person-years	21409	30763	42484	57221	77683	95510	109481	123105	125263
IR	0.7	0.7	1.2	0.7	1.0	0.4	0.7	0.9	1.5
95% CI	0.4–1.2	0.4–1.0	0.9–1.6	0.5–0.9	0.8–1.3	0.3–0.5	0.6–0.9	0.7–1.1	1.3–1.7

Figure 2. Incidence rate of RVGE hospitalizations from 2009 to 2017 seasons in the <5 and ≥ 5 –<10 years age groups.

IR: incidence rate; RVGE: rotavirus gastroenteritis; CI: confidence interval.

Table 1. The incidence rate ratio of RVGE hospitalizations for the post-vaccine period compared with the average for the pre-vaccine period (2009–2011 seasons) in the <5 and ≥ 5 –<10 years age groups.

Incidence rate ratio (vs. 2009–2011 average)	2012	2013	2014	2015	2016	2017
<5 years (age and gender-adjusted)						
IRR	0.94	1.06	0.31	0.39	0.33	0.37
95% CI	0.83–1.07	0.94–1.18	0.27–0.36	0.34–0.45	0.29–0.38	0.32–0.42
P-value ^a	0.332	0.341	<0.001	<0.001	<0.001	<0.001
≥ 5 –<10 years (unadjusted)						
IRR	0.81	1.25	0.45	0.85	1.07	1.81
95% CI	0.55–1.21	0.90–1.72	0.30–0.68	0.61–1.18	0.79–1.45	1.37–2.39
P-value ^a	0.308	0.181	<0.001	0.334	0.670	<0.001

IRR: incidence rate ratio; RVGE: rotavirus gastroenteritis; CI: confidence interval.

^aUsing Poisson regression model.

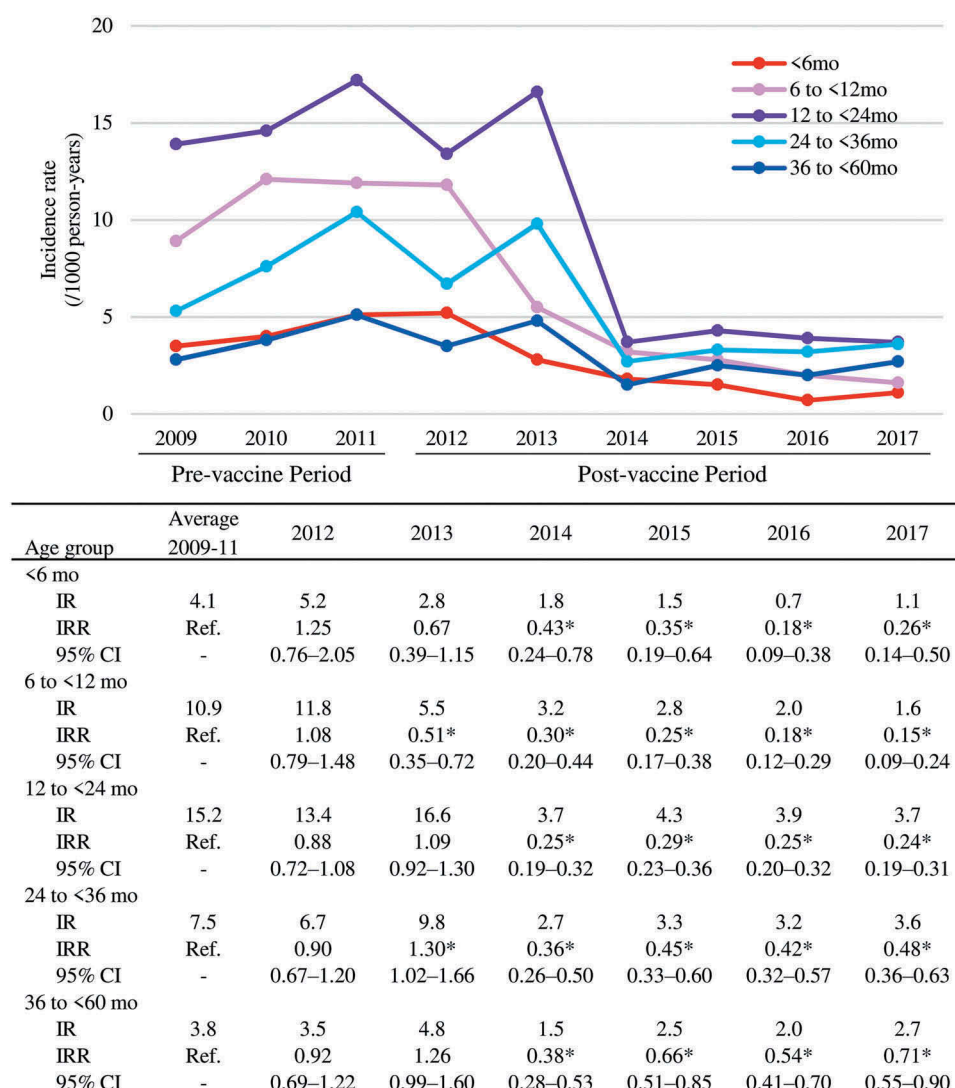


Figure 3. Incidence rate and incidence rate ratio of RVGE hospitalizations in five age groups.

IR: incidence rate; IRR: incidence rate ratio; RVGE: rotavirus gastroenteritis; mo: months; CI: confidence interval; Ref.: reference category; *: $P < .05$ with Poisson regression model.

consistent with those of our previous study¹⁰ and other reports in Japan.^{7-9,12} Additionally, the subsequent continuous reduction of hospitalizations until the 2017 season in this age group was demonstrated. In contrast, there was no apparent declining trend in the incidence of hospitalizations in children aged ≥ 5 -<10 years.

To our knowledge, this is the latest report describing the recent trend in RVGE hospitalizations in Japan, even for children aged <5 years, up to 2017. Following a sharp decline in the 2014 season for children aged <5 years, no further noticeable change in the incidence of RVGE hospitalizations was observed in our study, despite the continuous increase in vaccination coverage in Japan. This may be partially because of the gradual increase in vaccination coverage. The Ministry of Health, Labour and Welfare of Japan estimated that the national coverage of RV vaccine from 2012 to 2017 was 30.0%, 48.0%, 54.9%, 63.0%, 67.4%, and 72.1%, respectively (estimated from the total volume of vaccines distributed and

the number of live birth in the respective year considering the specified dose of each monovalent and pentavalent RV vaccine).⁶ In the US, it was not until a year after the vaccination coverage of children aged <1 year with at least one dose of vaccine reached 70% in 2009 that the reduction rate increased to over 80% in children aged <5 years.^{13,14} Contrastingly, in Finland, where pentavalent RV vaccine was introduced in a national immunization program in 2009 and vaccination coverage reached >95%, RVGE hospitalizations decreased quickly by over 80%.¹⁵ The decrease in Japan may have remained at 60%-70% for the duration of the study because of the moderate vaccination coverage. Additionally, the fluctuation in the incidence of RVGE hospitalizations, similar to that observed in the US,^{13,14} may have obscured the decline following the 2014 season in our study, even though the fluctuation was smaller in Japan. The incidence of RVGE hospitalizations is likely to fluctuate when the vaccination coverage is low to moderate.¹⁶ Under such

circumstances, susceptible children are thought to be pooled in the season with low incidence, possibly increasing the incidence in the subsequent season. In our study, after 2014, the incidence of RVGE hospitalizations slightly increased in the 2015 and 2017 seasons compared to that of the previous year (Figure 2), which may obscure a trend of decline after 2014.

In children aged ≥ 5 -<10 years, no apparent continuous declining trend of RVGE hospitalizations was observed following the introduction of RV vaccine. This is the first large scale report from Japan describing the trend of RVGE hospitalizations after vaccine introduction in children aged ≥ 5 years. The results were in contrast to those of previous reports from the US and UK describing a rapid decline in older (≥ 5 years) populations after RV vaccines were introduced in the national immunization program.^{14,17} Although it is apparent that most children in this age group would have remained unvaccinated as they were over the eligible age for vaccination, this was also the same case for previous studies from the US and UK. Thus, it is possible that vaccination coverage in the applicable age group in Japan might have been insufficient to provide a detectable indirect effect on the older age group. Unexpectedly, the incidence of RVGE hospitalizations in children aged ≥ 5 -<10 years was significantly high in the 2017 season compared with the pre-vaccine period. This could be explained simply by a fluctuation of the epidemic status; however, the following two possibilities should be carefully considered. Firstly, a decrease in RVGE in younger children may have reduced exposure of the children to the RV, resulting in an accumulation of those susceptible to RV in this age group. Secondly, RVGE in older children may have become more noticeable for pediatricians due to the substantial reduction of hospitalizations in younger children. This may have raised awareness of physicians on the presence of severe RVGE in older children, possibly enhancing the use of the RV rapid diagnosis kit. Further studies may be necessary to clarify the trend in RVGE in this age group.

There are some limitations to this study, as in our previous study.¹⁰ The first is that the specific socioeconomic background of the children in the employment-based health insurance claims database may limit the generalizability of the results. As the RV vaccine is self-financed in Japan, the vaccination status of children may be dependent on the economic or employment status of the parents. Thus, results of this study may not necessarily represent the full trend of RVGE hospitalizations in Japan. Next, it is impossible to directly infer a causal association between vaccination and disease reduction, primarily because the database lacks data on vaccine prescription and administration. Other limitations may be the possibility of misclassification of the diagnosis due to the use of the ICD-10 codes for our definitions, and the possible fluctuation in the epidemic status, although we used the three-year average incidence as the pre-vaccine incidence. Additionally, a change in physicians' attitudes towards the diagnosis of RVGE may have affected the incidence of RVGE hospitalizations, as stated above. Therefore, the results should be interpreted with caution. However, because the database includes 5% (over 490,000 children) of the entire population of Japan aged <10 years, one of the large databases available in Japan so far, a general trend in the incidence of RVGE hospitalizations could be obtained.

In conclusion, in this study, the incidence of RVGE hospitalizations among children aged <5 years in Japan during the RV season greatly declined in the post RV vaccine period in 2014, and the reduction was sustained until 2017. In children aged ≥ 5 -<10 years, no apparent continuous declining trend was observed from 2009 through 2017. Improved RV vaccination coverage may lead to a further reduction in severe RVGE in Japan.

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Disclosure of potential conflicts of interest

MK, MM, and AO are employees of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A., and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, N.J., U.S.A. MT has served as a paid lecturer for MSD K.K., Tokyo, Japan.

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