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Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children

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ABSTRACT

Background: Rotavirus (RV) vaccination has been available in Japan since November 2011, but is not yet part of Japan's national immunisation programs. There are insufficient data on vaccine effectiveness (VE) among Japanese children.

Methods: Between the months of January and May in 2014 and 2015, we conducted active surveillance of gastroenteritis among children at 14 medical facilities. Rectal swabs from all patients with diarrhoea or vomiting were tested for RV by immunochromatography, and positive specimens were genotyped. Demographic data and immunisation records were obtained from a questionnaire completed by their parents/guardians or medical records. A test-negative case-control design was used to examine vaccine effectiveness (VE) using unconditional logistic regression analysis adjusted for possible confounding factors.

Results: Among the 1519 eligible subjects (children with acute gastroenteritis symptoms aged ≥2 months to <3 y visiting medical facilities) recruited, 487 cases and 925 controls were enrolled. Cases had more severe symptoms than controls, requiring more intensive treatment, including intravenous rehydration or hospitalisation. VE against all rotavirus gastroenteritis (RVGE) was 80.0% (95% confidence interval [CI], 72.8–85.5%), and VEs against RV1 and RV5 were similar, at 80.6% (95%CI, 70.7–87.1%) for RV1 and 80.4% (95% CI, 69.1–87.6%) for RV5. Although VEs of both vaccines decreased with age, VEs against all RVGE were >70% up to 2 years after vaccination. VEs increased with severity of RVGE, and VE against severe RVGE, requiring intravenous rehydration or hospitalisation, was 97.3% (95% CI, 88.8–99.3%). VEs of RV1 and RV5 against G1P[8] and G2P[4] were comparable, at RV1, 89.8% (95% CI, 78.2–95.5%) and 78.3% (95% CI, 23.6–93.8%); and RV5, 85.8% (95% CI, 72.8–92.6%) and 88.1% (95% CI, 10.1–98.4%), respectively.

Conclusions: Rotavirus vaccines were effective in preventing mild to severe RVGE, irrespective of vaccine type, time since vaccination, or RV genotype.

1. Introduction

Rotavirus (RV) is a common cause of severe gastroenteritis among infants and young children aged <5 years. It causes diarrhoea and vomiting, and can cause fatal dehydration, especially in developing countries [1]. Since 2006, two live oral vaccines, a monovalent human rotavirus vaccine (RV1, Rotarix®, GlaxoSmithKline Biologicals, Rixansart, Belgium) and a pentavalent bovine-human reassortant vaccine (RV5, RotaTeq®, Merck & Co., Inc., Rahway NJ, USA) have been licensed in >100 countries [2,3]. The World Health Organization (WHO) recommends these vaccines for national immunisation programs (NIP) [4]. Globally, 86 countries had developed NIPs by September 2016 [5].

Despite the WHO recommendations [4], and the effectiveness [6,7], safety [8], and impact of the RV vaccines against RV-related death [9,10] or hospitalisation [10], many countries in Asia, including Japan, have not yet introduced RV1 or RV5 into their NIPs [5]. The disease burden, severity of disease, vaccine efficacy or vaccine effectiveness (VE), and vaccine safety are generally addressed in the decision-making process of introducing a vaccine into an NIP [11]. Following clinical trials in Japan [12,13], RV1 and RV5 became available on the private market in November 2011 and July 2012,

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respectively. Before the introduction of RV vaccines in Japan, RVGE-related hospitalisation among children aged <5 y was estimated to be 7.9–17.6 hospitalisations/1000 person-years, 2–5 times higher than that in other developed countries (before the advent of the vaccine), although fatal cases were rare [14]. Recently, substantial declines in RVGE incidence [15] and RVGE hospitalisation cases were reported in the post-licensure period [16]. A case-control study using a test-negative design showed that vaccine effectiveness (VE) against hospitalisation due to RVGE among children <5 y was 70.4% in Japan [17]. However, VE against RVGE according to disease severity, virus genotype, vaccine type, and duration after vaccination have not been fully evaluated in Japan. Because the disease burden, epidemic virus type, and vaccination coverage are different in different countries, evaluation of VE by each country is needed. Without such evidence it is difficult for health decision makers to decide upon introduction of RV vaccine into their country's NIP.

The present study was conducted to evaluate the VE of RV against RVGE according to vaccine type, duration of protection, RVGE severity, and RV genotype among children aged <3 y in Japan.

2. Materials and methods

2.1. Study design and setting

We evaluated the VE of rotavirus vaccines using a WHO test-negative design, which is commonly used for assessing VE against rotavirus [18]. We conducted active surveillance of gastroenteritis among children ≥2 months to <3 years. All patients presenting to a medical facility for acute gastroenteritis were enrolled. The study was conducted between 1st January and 31 May in both 2014 and 2015. According to the National Epidemiological Surveillance of Infectious Diseases, Japan, this period correlates with the peak rotavirus epidemic data reported by a national infection research institute [19]. The investigation areas were Saga and Fukuoka prefectures. In most of these areas, rotavirus vaccination is voluntary, costing ¥13000–15000 (€96.7–111.6) per inoculation. We requested the cooperation of 14 medical facilities (12 clinics and 2 hospitals). Clinics were paediatric outpatient departments with weekday hours, and hospitals included paediatric outpatient, inpatient, and emergency departments. The survey protocol was approved by the Ethical Committees of Saga University Faculty of Medicine and Saga-ken Medical Centre Koseikan. Other facilities were approved as cooperating institutions of the Saga University Faculty of Medicine.

2.2. Patient recruitment and case/control definition

Children, ≥2 months to <3 y, visiting the target medical facilities for acute gastroenteritis, whose parents or guardian gave consent according to the rules of the Declaration of Helsinki to this study, were eligible for recruitment. Acute gastroenteritis was defined as two or more diarrhoea (looser-than-usual stool or liquid stools or frequent stools) during the preceding 24 h or vomiting (excluding coughing with vomiting). Children were excluded if their symptom onset occurred within 14 days of rotavirus vaccination (immunization status was available from records in 98% of patients; 2% were from parent/guardian verbal report) or they had a history of previous rotavirus infection before presentation. Stool samples were collected by rectal swabs from all eligible children and tested initially for rotavirus via an immunochromatographic assay (ICA, ImmunoCard® SD Rota/Adeno, Standard Diagnostics, Inc., Yongin-si, South Korea) at each facility. The sensitivity and specificity of ICA were 100% and 99.7%, respectively [20]. Even if the initial symptom was vomiting only and diarrhoea appeared after the visit, all rectal swabs were tested for rotavirus. Stool samples obtained at study recruitment were stored at −20 °C after testing in each medical facility, and positive samples were sent to Sapporo Medical University for genotyping.

2.3. Data collection

The following data were obtained by means of a self-administered questionnaire completed by each child's parents or guardian during the visit: sex, date of birth, birth weight, current breastfeeding (yes/no), receipt of day care service, number of family members in the home, number of siblings in the home, parents/guardian age(s), underlying illnesses (food allergy, asthma, atopic dermatitis, epilepsy, otolaryngologic disease, digestive disease, heart disease, Kawasaki disease, febrile convulsions, immunodeficiency, and congenital deformity), history of RVGE, history of rotavirus vaccination, number of doses, date of the last dose and type of vaccine (if vaccinated), clinical symptoms (diarrhoea, vomiting, fever, seizures), and date of symptom onset. In Japan, vaccination history is usually recorded in a maternal and child health handbook maintained by individuals. Thus, the information collected about vaccination status was verified using the record. When missing answers or illogical data were detected, accurate data were obtained by telephone interview with the parent/-guardian. In addition, we also obtained the following clinical findings from medical records in the medical facilities in cooperation with paediatricians: detailed clinical symptoms, date at diagnosis, and treatment (oral medication, intravenous rehydration to correct dehydration, hospitalisation). Unless there was a second visit for the acute illness, within 1–2 months after the subjects' outpatient visit we telephoned their parents/guardians to assess when their symptoms had resolved, and whether they had taken the child to a different facility for further treatment.

2.4. Severity classification

To assess the severity of disease in the outpatient setting, we adopted three of seven variables in the modified Vesikari score [21] (MVS) (severity score): (1) maximal number of diarrhoeal stools per 24 h period (0 points: none, 1 point: 1–3, 2 points: 4–5, 3 points: ≥6), (2) maximal number of vomiting episodes per 24 h period (0 points: none, 1 point: 1, 2 points: 2–4, 3 points: ≥5), and (3) maximal fever (recorded at the facility or at home) (0 points: <37.0 °C, 1 point: 37.1–38.4 °C, 2 points: 38.5–38.9 °C, 3 points: ≥39.0 °C). The symptoms of all enrolled patients were scored, and disease severity was classified into three categories (mild severe: 1–4, moderate severe: 5–6, and severe: 7–9 in total score).

2.5. Rotavirus genotypes

Double-stranded RNA was extracted from stool suspensions of cases in assay diluent using a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany). Reverse transcription-polymerase chain reaction (RT-PCR) was performed as previously described [22] using conventional G and P genotyping primers [23,24]. Briefly, reverse transcription was performed using reverse transcriptase (SuperScript II®, Invitrogen, Carlsbad CA, USA) at 45 °C for 45 min followed by 94 °C for 3 min. Polymerase chain reaction (PCR) was performed using a DNA polymerase (GoTaq Flexi DNA polymerase®, Promega, Madison WI, USA) in a thermal cycler (SimpliAmp®, Applied Biosystems, Foster City CA, USA) under the following conditions: initial denaturation at 95 °C for 15 min; 40 cycles at 94 °C for 45 s, 50 °C for 45 s, and 70 °C for 2.5 min; and

a final extension at 70 °C for 7 min. The G and P genotypes were determined by the size of the second PCR products.

2.6. Statistical analysis

Primary analysis assessed the effectiveness against any severity of RVGE of at least one dose of either vaccine, full doses of RV1 (two doses) or RV5 (three doses), or partial vaccination (one dose of RV1 and one or two doses of RV5), compared with no vaccination. Subgroup analyses were performed to estimate (1) the duration of protection after vaccination by measuring effectiveness among children 6–11 months, 1 y, and 2 y of age, (2) potential differences in protection against RVGE according to severity and treatment, and (3) strain-specific protection.

We first performed bivariate analyses to assess differences in indicators of the background characteristics, clinical symptoms, and treatment between cases and controls using the chi-squared test or Wilcoxon rank sum test. Background characteristic variables that exhibited a $P < .05$ or appeared to be medically related to the disease were considered potential confounders for adjustment. Unconditional logistic regression models were constructed to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). We employed the following continuous and categorical variables for adjustment: age (months), use of day care (yes/no), having siblings (yes/no), current breastfeeding (yes/no), facility (12 clinics/2 hospitals), onset year (2014/2015), and severity score (1–4, 5–6, and 7–9). For sensitivity analysis, we further adjusted for year and month of birth, creating six categories: January–June 2012, July–December 2012, January–June 2013, July–December 2013, January–June 2014, and July 2014–February 2015. We included this as a possible confounding factor. VE was calculated as $(1 - \mathrm{OR}) \times 100$ (%). Commercial software (Ver. 9.3 for Windows; SAS Institute, Cary, NC, USA) was used for statistical analysis.

3. Results

Of a total of 1516 patients, the parents/guardians of 1488 (98.1%) consented to participate in this study and responded to the questionnaire. Of these, we excluded 76 patients (5.1%) who did not meet the inclusion criteria, leaving a final group of 1412, including 487 cases and 925 test-negative controls (Fig. 1).

Table 1 shows the characteristics, clinical symptoms, and treatment of cases and controls. The mean severity score of all 1412 patients was 3.42, and the scores in the top 10% and 25% of all patients were ≥7 and ≥5, respectively. Based on this result, we defined the severity of disease according to the following severity score: 1–4 mild, 5–6 moderate, and 7–9 severe. The proportion of subjects with severe symptoms was significantly higher in cases than in controls. In total, progress following outpatient visits could be confirmed for 1010 patients (395 cases and 615 controls). Cases more commonly required extensive treatment, including intravenous rehydration and hospitalisation, than controls.

After adjustment for potential confounders, the VE against any severity of RVGE was calculated at 80.0% (95% CI, 72.8–85.5). The VE was similar for full doses of the two vaccines; partial vaccination provided lower protection than full vaccination (Table 2).

Table 3 shows VE according to age by vaccine type. Because only seven cases were fully vaccinated by 6–11 months of age, we considered the VE of the two vaccines together. Although the VE declined over time following vaccination, the effect persisted at 24–35 months of age.

Table 4 shows VE by symptom severity or clinical treatment. The VE against RVGE with a severity score of 5–6 was 85.9% (95% CI, 76.2–91.6) and that for a severity score of 7–9 was 91.4% (95% CI, 78.1–96.6). Among children with complete clinical information

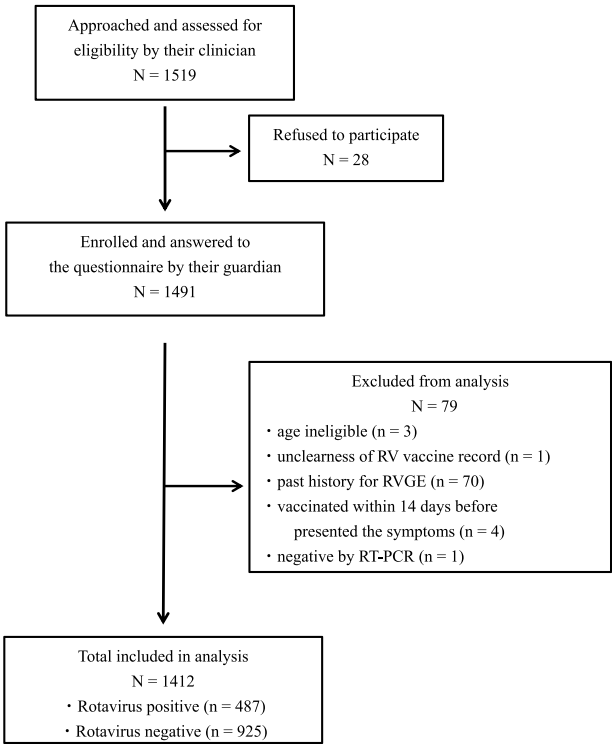

Fig. 1. Flow diagram for the enrollment of cases and controls (January to May 2014 and 2015).

for treatment, only two vaccinated cases (0.5%) required intravenous rehydration, and none needed hospitalisation. The VE for patients needing intravenous rehydration or hospitalisation due to RVGE was 97.3% (95% CI, 88.8–99.3).

The rotavirus genotype was identified in 99.8% (487/488) of rotavirus-positive specimens. The most common rotavirus GP genotype was G1P[8], which was detected in 235 strains (48.2%), followed by G9P[8] (175; 35.9%) and G2P[4] (35; 7.2%) (Supplemental Table 1). The VEs of RV1 and RV5 against G1P[8] were 89.8% (95% CI, 78.2–95.5) and 85.8% (95% CI, 72.8–92.6), and those against G2P[4] were 78.3% (95% CI, 23.6–93.8) and 88.1% (95% CI: 10.1–98.4), respectively. The VE against G9P[8] was lower for both vaccines compared to that against G1P[8] and G2P[4] (Table 5). Results from sensitivity analyses, including adjustments for year and month of birth, were comparable to the above VEs (Supplemental Tables 2–5).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.007.

4. Discussion

We demonstrated the effectiveness of RV vaccines according to vaccine type, time interval after vaccination, disease severity, and virus genotype in Japan, using a case test-negative control design. RV vaccines were highly effective against severe RVGE needing intravenous rehydration or hospitalization (VE was 97.3% [95% CI: 88.8–99.3]) and mild-to-moderate RVGE (VE was 78.7% [68.9–85.4] for mild RVGE and 85.9% [76.2–91.6] for moderate RVGE). The VEs of RV1 and RV5 against any genotype of RVGE were comparable. These levels of effectiveness were similar to those reported by previous clinical trials [12,13], confirming the effectiveness of rotavirus vaccines in the real-world setting in Japan. In addition, although it waned somewhat with age, VE was >70%

Table 1
Baseline characteristics, clinical symptoms, and treatment of cases and controls.

Variables	Cases, n = 487 Rotavirus-positive		Controls, n = 925 Rotavirus-negative		*P* value[a]
Demographics					
Age at onset, median months [range]	19	[2–35]	15	[2–35]	<.01
Sex: males, n (%)	269	(55.2)	503	(54.4)	0.76
Location of hospital, n (%)					0.14
Saga	347	(71.2)	693	(74.9)	
Fukuoka	140	(28.8)	232	(25.1)	
Onset year, n (%)					<.01
2014 season	64	(13.1)	262	(28.3)	
2015 season	423	(86.9)	663	(71.7)	
Additional history					
Underlying condition: Yes, n (%)	83	(17.0)	146	(15.8)	0.54
Premature (BW > 2500 g) [b], n (%)	438	(90.7)	811	88.3	0.18
Use of day care : Yes, n (%)	320	(66.4)	482	(52.5)	<.01
Siblings: Yes, n (%)	319	(65.5)	554	(59.7)	0.03
No. of siblings, median [range]	1	[1–7]	1	[1–6]	0.18
Age of parents, median years [range]					
Mother[c]	32	[19–46]	32	[18–48]	0.35
Father[d]	34	[20–57]	34	[20–62]	0.67
Breastfed[e]: Yes, n (%)	143	(29.6)	405	(44.1)	<.01
Systemic symptoms before receiving the medical examination					
Diarrhea, n (%)	460	(94.5)	805	(87.0)	<.01
No. of diarrheal stools, median [IQR]	4	[2–6]	3	[2–6]	0.15
Vomiting, n (%)	368	(75.6)	412	(44.5)	<.01
No. of vomiting episodes, median [IQR]	3	[2–5]	2	[1–4]	<.01
Fever, n (%)	340	(69.8)	364	(39.4)	<.01
Max recorded fever, median [IQR]	38.5	[37.9–39.0]	38.0	[37.6–38.9]	0.02
Seizure[f] (in the course of disease), n (%)	8	(2.0)	4	(0.7)	0.07
Severity of disease[g], n (%)					<.01
Mild severe	256	(52.6)	80.1	(86.6)	
Moderate severe	162	(32.3)	103	(11.1)	
Severe	69	(14.1)	21	(2.3)	
Treatment[h], n (%)					<.01
Outpatient (oral treatment)	320	(81.0)	594	(96.6)	
Outpatient (intravenous rehydration)	64	(16.2)	16	(2.6)	
Hospitalisation	11	(2.8)	5	(0.8)	

Abbreviations: SD, standard deviation; IQR, Interquartile Range.
[a] Chi-squared test or Wilcoxon's rank-sum test was used as appropriate.
[b] Analyses were based on data from 483 cases and 919 controls.
[c] Analyses were based on data from 482 cases and 919 controls.
[d] Analyses were based on data from 485 cases and 919 controls.
[e] Analyses were based on data from 459 cases and 909 controls.
[f] Analyses were based on data for children younger than 12 months old (n = 383).
[g] Severity of disease was assessed using the severity score (see the Methods section) "mild severe" corresponds to a total score of 1–4, "moderate severe" corresponds to 5–6, and "severe" corresponds to 7–9.
[h] Analyses were based on data from patients for whom confirmation of the outcome was possible (cases/control = 395/615).

Table 2
Vaccine effectiveness against rotavirus disease.

	Cases		Controls		Crude OR	Adjusted OR[b]	VE(%)	95% CI(%)
	n	(%)	n	(%)				
Unvaccinated	420	(86.2)	498	(53.8)	1[c]	1[c]		
Vaccinated (≥1 dose)	67	(13.8)	427	(46.2)	0.19	0.20	80.0	72.8–85.5
Partial vaccination[a]	4	(0.8)	22	(2.4)	0.30	0.33	67.2	−3.7–89.6
Full dose vaccination								
RV1 2 doses	36	(7.4)	226	(24.4)	0.19	0.19	80.6	70.7–87.1
RV5 3 doses	27	(5.5)	179	(19.4)	0.18	0.20	80.4	69.1–87.6

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1, monovalent; RV5, pentavalent.
[a] Received one or two doses of RV5 or one dose of RV1.
[b] Adjusted for age in months, use of day care, having siblings, breastfeeding, severity score, facility, and onset year.
[c] Reference category.

2 y after vaccination. These results are pivotal evidence in favour of the introduction of RV vaccine into the Japanese NIP.

The strength of this study was that VE was evaluated according to the vaccine type and RV genotype. The effectiveness of RV1 against RVGE of G2P[4] strains has been a concern because genotypes of all 11 genes of G2P[4] are typically different from those of G1P[8] strains [25]. However, despite being slightly less effective than the 88.1% of VE of RV5, the 78.3% VE of RV1 proves its worth against G2P[4] in our study. These data are compatible with previous reviews in other developed countries. The pooled VEs of RV1 and RV5 against severe RVGE attributed to G2P[4] were 87% (95% CI, 76–93) and 82% (95% CI, 70–89), respectively [26]. In

Table 3
Vaccine effectiveness against rotavirus disease in Japan according to age.

		Cases		Controls		Crude OR	Adjusted OR[b]	VE	95% CI (%)
Age		n	(%)	n	(%)				
6–11 months	Unvaccinated	53	(88.3)	141	(52.6)	1[c]	1[c]		
	Full-dose vaccination[a]	7	(11.7)	123	(45.9)	0.15	0.14	85.8	64.3–94.3
12–23 months	Unvaccinated	233	(87.9)	240	(54.7)	1[c]	1[c]		
	RV1 2 doses	14	(5.3)	103	(23.5)	0.14	0.16	84.5	70.6–91.8
	RV5 3 doses	17	(6.4)	90	(20.5)	0.20	0.17	83.0	68.7–90.7
24–35 months	Unvaccinated	129	(82.2)	88	(54.0)	1[c]	1[c]		
	RV1 2 doses	15	(9.6)	50	(30.7)	0.21	0.24	75.7	51.4–87.8
	RV5 3 doses	10	(6.4)	25	(15.3)	0.27	0.29	70.8	32.2–87.4

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1, monovalent; RV5, pentavalent.
[a] Received two doses of RV1 or three doses of RV5.
[b] Adjusted for use of day care, having siblings, breastfeeding, severity score, facility, and onset year.
[c] Reference category.

Table 4
Vaccine effectiveness against rotavirus disease in Japan by severity of symptoms or clinical treatment.

	Cases		Controls		Crude OR	Adjusted OR[c]	VE(%)	95% CI(%)
	n	(%)	n	(%)				
	Mild severe[b]							
Unvaccinated	213	(83.2)	498	(53.8)	1[d]	1[d]		
Full-dose vaccination[a]	40	(15.6)	405	(43.8)	0.23	0.21	78.7	68.9–85.4
	Moderate severe[b]							
Unvaccinated	143	(88.3)	498	(53.8)	1[d]	1[d]		
Full-dose vaccination[a]	18	(11.1)	405	(43.8)	0.16	0.14	85.9	76.2–91.6
	Severe[b]							
Unvaccinated	64	(71.1)	498	(53.8)	1[d]	1[d]		
Full-dose vaccination[a]	5	(5.6)	405	(43.8)	0.10	0.09	91.4	78.1–96.6
	Requiring intravenous Rehydration							
Unvaccinated	61	(15.4)	295	(48.0)	1[d]	1[d]		
Full-dose vaccination[a]	2	(0.5)	302	(49.1)	0.03	0.03	96.8	86.8–99.2
	Requiring hospitalisation							
Unvaccinated	11	(1.8)	295	(48.0)	1[d]	1[d]		
Full-dose vaccination[a]	0	(0.0)	302	(49.1)	0	0	100	Not estimated

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1,monovalent; RV5, pentavalent.
[a] Received two doses of RV1 or three doses of RV5.
[b] Severity of disease was assessed with severity score (see the Methods section).''mild severe" corresponds to a total score of 1–4, ''moderate severe" corresponds to 5–6, and ''severe" corresponds to 7–9.
[c] Adjusted for age in months, use of day care, having siblings, breastfeeding, facility, and onset year.
[d] Reference category.

Table 5
Vaccine effectiveness against rotavirus disease in Japan by genotype.

	Cases		Controls		Crude OR	Adjusted OR[a]	VE(%)	95% CI(%)
	n	(%)	n	(%)				
	With G1P[8] strains							
Unvaccinated	212	(18.3)	498	(53.8)	1[b]	1[b]		
RV1 2 doses	8	(0.7)	226	(24.4)	0.08	0.10	89.8	78.2–95.5
RV5 3 doses	12	(1.0)	179	(19.4)	0.16	0.14	85.8	72.8–92.6
	With G9P[8] strains							
Unvaccinated	138	(12.5)	498	(53.8)	1[b]	1[b]		
RV1 2 doses	22	(2.0)	226	(24.4)	0.35	0.32	67.8	45.7–80.9
RV5 3 doses	13	(1.2)	179	(19.4)	0.26	0.33	67.5	39–82.7
	With G2P[4] strains							
Unvaccinated	31	(3.2)	498	(53.8)	1[b]	1[b]		
RV1 2 doses	3	(0.3)	226	(24.4)	0.21	0.22	78.3	23.6–93.8
RV5 3 doses	1	(0.1)	179	(19.4)	0.09	0.12	88.1	10.1–98.4

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; CI, confidence interval; RV1, monovalent; RV5, pentavalent.
[a] Adjusted for use of day care, having siblings, breastfeeding, severity score, facility, and onset year.
[b] Reference category.

contrast, the effectiveness of both vaccines against G9P[8] was low. In addition to temporal and regional differences in rotavirus genotype [27], the improvement of vaccine coverage may induce changes in the dominant genotype and the appearance of reassortant mutant strains. Therefore, long-term observation of the rotavirus genotype distribution will be necessary.

In general, the VEs for RVGE are higher in developed countries than in developing countries, irrespective of disease severity [28]. For example, VE against RVGE not requiring hospitalisation in Spain was 83.5% (95% CI, 25.4–96.3) [29] compared to 64% (95% CI, 24–83) in Malawi [30]. The VE for RVGE may also be affected by whether vaccination is provided as part of a country's NIP or not, because vaccination under NIP can attain higher vaccine coverage than vaccination paid for out-of-pocket. However, the VEs against severe RVGE in countries where RV vaccination is paid for out-of-pocket [29,31–33] have been similar to those in countries where RV vaccination is under NIP [34]. Our findings are analogous to those in developed countries where RV vaccination is paid for out-of-pocket.

In relation to the duration of protection after vaccination, Immergluck et al. [34–36] reported no evidence of waning of protection from RV1 and RV5 beyond 24 months of age. Conversely, Correia et al. [37] found that VE declined among children aged ≥12 months. Although the VE decreased over time, VE against RVGE was >70% in children aged 24–35 months in our study. In Japan, before the introduction of rotavirus vaccines, 70% of cases of RVGE requiring hospitalisation in children <5 y were <2 y [14]. This result indicates that rotavirus vaccination is particularly protective against severe RVGE in children aged <2 y in this country.

Several reports have evaluated the disease burden for RVGE hospitalisation [14,38], and a recent study has examined the impact of RV vaccine introduction on RVGE hospitalisation in Japan [16]; however, disease burden data for RVGE outpatient visits are still lacking. Only one study reported the age-specific annual incidence of RVGE outpatient visits before 2000, before RV vaccine was introduced [38]. According to Yokoo et al., the age-specific annual incidence of RVGE outpatient visits before RV vaccine was introduced were 151.3 per 1000 infants of 6–11 months and 270.7 per 1000 children of 12–23 months [38]. Given the results of our study, with 85.8% VE among infants 6–11 months old and the 83.0%–84.5% VE among children 12–23 months old, the rate of RVGE cases would be expected to decrease to 21.2 per 1000 infants 6–11 months, and 43.3–46.0 per 1000 children aged 12–23 months, if all infants received the RV vaccines. In fact, a substantial reduction in the disease burden of RVGE incidence after RV vaccine introduction was observed in national surveillance data of Infectious Agents Surveillance Reports (laboratory-confirmed RV pathogen) [15,19,39]. During the 2010/2011 to 2012/2013 seasons (from October to September), before RV vaccine had been introduced, the number of laboratory-confirmed RV infections was 908–940, while it was 435 in the 2013/2014 season (from October to September) after its introduction.

This study has some limitations. First, we used our original independent score to compare severity. MVS is useful for assessing the severity of acute gastroenteritis, and it is also used in clinical trials [12]. However, it is difficult to compare severity using MVS, which incorporates the durations of diarrhoea and vomiting [21], because many target children visit medical facilities and receive treatment during the early disease stage. We adopted parts of the MVS and scored each symptom at the time of the outpatient visit. Severity was determined by the score distribution of all patients, and this was considered sufficiently valid. Second, most of the target medical facilities were limited to primary care facilities. If symptoms are severe, patients tend to visit not a clinic but a hospital to receive more aggressive treatment. In the 2012/13 season, we targeted higher-order medical institutions and evaluated the VE of rotavirus vaccines retrospectively [40]. The effectiveness for hospitalised patients was 88.8% (95% CI, 34.3–100.0). That finding coincides with our present results in that the VE of rotavirus vaccines was higher among cases of severe illness. Finally, this study targeted medical facilities in Saga and Fukuoka prefecture in the 2015 and 2016 seasons, and it is a concern whether the same results would be obtained in other seasons or areas, because vaccination coverage and endemic virus genotype might vary. The Ministry of Health, Labour and Welfare published rotavirus vaccine coverage data by prefecture in April 2013. Vaccine coverage in Saga and Fukuoka prefectures totalled 28% and 40%, respectively, which were lower than those in other prefectures. However, our findings are similar to those in developed countries, and confirm the efficacy of rotavirus vaccines in Japan.

5. Conclusions

Rotavirus vaccines were effective in preventing not only severe RVGE, but also mild and moderate RGVE, irrespective of vaccine type or RV genotype. The highly protective effect lasted well over 2 y.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

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