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# Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children

Kaoru Araki [a,b,*], Megumi Hara [a], Takeshi Tsugawa [c], Chisato Shimanoe [a], Yuichiro Nishida [a], Muneaki Matsuo [b], Keitaro Tanaka [a]

[a] Department of Preventive Medicine, Faculty of Medicine, Saga University Saga, Japan
[b] Department of Pediatrics, Faculty of Medicine, Saga University Saga, Japan
[c] Department of Pediatrics, Sapporo Medical University School of Medicine Hokkaido, Japan

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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,

* Corresponding author at: Department of Preventive Medicine, Faculty of Medicine, Saga University Saga, Japan.
*E-mail address:* e5814@cc.saga-u.ac.jp (K. Araki).

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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

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