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Original Article

Changes in Rotavirus Genotypes before and after Vaccine Introduction: a Multicenter, Prospective Observational Study in Three Areas of Japan

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SUMMARY: In Japan, monovalent and pentavalent rotavirus (RV) vaccines were approved in 2011 and 2012, respectively. To monitor changes in the RV genotypes before and after vaccine introduction, we performed a prospective observational study among children (< 5 years) with gastroenteritis who tested RV-positive on antigen rapid tests. Stool samples were collected from 3 different sites in Japan: Tsu City, Mie Prefecture; Kurashiki City, Okayama Prefecture; and Isumi City, Chiba Prefecture. RV genotypes were determined using reverse transcription-polymerase chain reaction. In Tsu City, G3P[8] was dominant (61.0–77.1%) before vaccine introduction, but decreased after introduction. Meanwhile, in an inverse proportion to the decrease in G3P[8], G1P[8] increased until the 2013/14 season, when a sudden predominance of G2P[4] (100%) occurred. A similar trend was observed in Kurashiki City in terms of the extent of reduction in G3P[8] and the emergence of G2P[4]. In Isumi City, G1P[8] was dominant (70.3%) before vaccine introduction, and G9P[8] became predominant (83.3%) in the 2013/14 season. To determine whether the genotype changes are attributable to vaccines or natural epidemiological changes, ongoing continuous monitoring of the RV genotypes is required.

INTRODUCTION

Group A rotavirus (RV) infection is the primary cause of severe gastroenteritis in children less than 5 years of age, especially infants (1). Since 2006 when they were introduced, live attenuated RV vaccines have been part of the national immunization programs of various countries (2), and the efficacy and safety of these vaccines have been confirmed in many countries (3–5). In 2009, the World Health Organization recommended that all nations include an RV vaccine in their national immunization programs (1). However, in Japan, the attenuated monovalent (G1P[8]) human rotavirus vaccine (RV1; Rotarix®) was not approved until November 2011, and the pentavalent (G1, G2, G3, G4, and P[8]) human-bovine rotavirus reassortant vaccine (RV5; RotaTeq®) was not approved until July 2012. Hence, these are not currently included as routine vaccinations in the Japanese childhood immunization program.

In 1999, acute gastroenteritis was designated as a category V notifiable disease under the Communicable Diseases Prevention Law in Japan (6). This law requires approximately 3,000 designated pediatric sentinel sites to report the total number of patients, and their sex and age group on a weekly basis (7); all of these case data are condensed into the National Epidemiological Surveillance of Infectious Diseases (NESID) system. Because the cause of acute gastroenteritis was not required to be reported to the NESID in 2007, we established the Rotavirus Epidemiology Study Group (RESG) with the aim of understanding the true epidemiology and disease burden of RV gastroenteritis among children less than 5 years of age in Japan. This group consists of one laboratory and 5 medical facilities in 3 different locations throughout Japan. We collect demographic information, clinical symptoms, and stool samples from RV gastroenteritis patients with a positive rapid test result. The RESG has conducted a retrospective study (2003–2007) and a prospective active surveillance study (2008–2009) among inpatients with RV gastroenteritis in Mie Prefecture, Japan. The results of these studies have shown that the disease burden of hospitalization for RV gastroenteritis in Japan is comparable to that of other developed countries (8,9). Our group has continued to conduct studies on RV vaccine efficacy and cost-effectiveness with respect to the introduction of RV vaccines into the national immunization program.

In our abovementioned studies, stool samples that were collected, were sent to the laboratory and underwent polymerase chain reaction (PCR) and genotype testing to confirm RV infection as well as the RV geno-

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type. In countries where RV vaccines were introduced earlier than in Japan, studies have reported that different distributions of RV genotypes were observed before and after introduction of the RV vaccine (10). However, whether this change is attributable to the protective effect of vaccines or to natural epidemiological changes remains controversial. Therefore, continuous monitoring of changes in the RV genotypes is necessary to evaluate the influence of RV vaccines. Here, we summarize the results of the RV genotype changes in Japan before and after vaccine introduction.

MATERIALS AND METHODS

Study sites and period: Five different medical facilities and one laboratory participated in this study (Fig. 1). Stool samples were collected from inpatients at 2 hospitals in Tsu City, Mie Prefecture (National Mie Hospital, Mie Chuo Medical Center), from the 2007/08 to 2013/14 seasons. Samples were also collected from an outpatient clinic in Tsu City (Umemoto Children's Clinic); an outpatient clinic in Isumi City, Chiba Prefecture (Sotobo Children's Clinic); and from inpatients and outpatients treated at a hospital in Kurashiki City, Okayama Prefecture (Kawasaki Medical School Hospital), from the 2010/11 to 2013/14 seasons.

The annual number of births (2013) and the number of children younger than 5 years old (2010) in each city were 2,291 and 11,755 in Tsu City, 203 and 1,206 in Isumi City, and 4,561 and 22,058 in Kurashiki City, respectively (11).

Study design: We conducted a prospective observational study of RV genotypes using stool samples from children (<5 years old) with RV gastroenteritis who presented to a group of hospitals in Tsu City, Mie Prefecture, Japan, from the 2007/08 through 2013/14 seasons (one season is defined as the period between November and October of the following year). Gradually, the study site was expanded to include clinics in Tsu City and hospitals and clinics located in 2 other areas, Okayama and Chiba, for the 2010/11 to 2013/14 seasons.

Naturally defecated stool specimens were collected from children younger than 5 years old who had diarrhea (3 or more loose, watery stools within the preceding 24 hours) or vomiting (once or more within 24 hours), had been given a diagnosis of acute gastroenteritis by a physician, and had a positive stool RV antigen rapid test result. At the 2 hospitals in Tsu City (Umemoto Children's Clinic and Sotobo Children's Clinic), stool samples were tested using a commercially available enzyme immunoassay kit (Rapid-testa; Sekisui Medical Co., Tokyo, Japan); its sensitivity and specificity are approximately 100% and 99.3%, respectively, as compared with PCR (data from package insert). At Kawasaki Medical School Hospital, samples were tested with a commercially available enzyme immunoassay kit (ImmunoCard ST; Fujirebio Inc., Tokyo, Japan); its sensitivity and specificity are approximately 93.1% and 95.8%, respectively, as compared with electron microscopy (data from package insert).

Stool samples were not collected if the parent or guardian of each participant did not sign the study consent form. In the outpatient setting, we asked parents or caregivers to bring a stool specimen if their children had gastrointestinal symptoms; however, we did not actively collect stool samples, such as with use of enema. Patients were excluded from the study if the stool sample volume was insufficient for G and P genotyping.

After introduction of the RV vaccine in November 2011, we interviewed parents or guardians of participants about their history of RV vaccination, including the types and dates of vaccination, to evaluate the possible influence of vaccine on the genotype distribution.

G and P genotyping: RV-positive stool samples were stored at −80°C on site and transported in a frozen state to the Department of Virology and Parasitology, Fujita Health University School of Medicine, for gene analysis.

The RV G and P types were determined using reverse transcription-polymerase chain reaction, as described previously (12,13). First, phosphate-buffered saline was added to the stool sample to generate a 10% stool suspension, and the supernatant was obtained by low-speed centrifugation. Thereafter, viruses were decomposed using destruction solution (sodium dodecyl sulfate, 2-mercaptoethanol, ethylenediaminetetraacetic acid), and ribonucleic acid (RNA) was extracted using treatment with chloroform and ethanol sedimentation (12). For G typing, the full-length *VP7* gene was amplified using a pair of primers, 5′–GGCTTTAAAAGAGAGAATTTCCGTCTGG–3′ (T31) and 5′– GGTCACATCATACAATTCTAATCTAAG–3′ (T32), corresponding to the common 5′ end (strain Wa) and 3′ end (strain SA11) of the *VP7* gene, respectively. In the second PCR am-

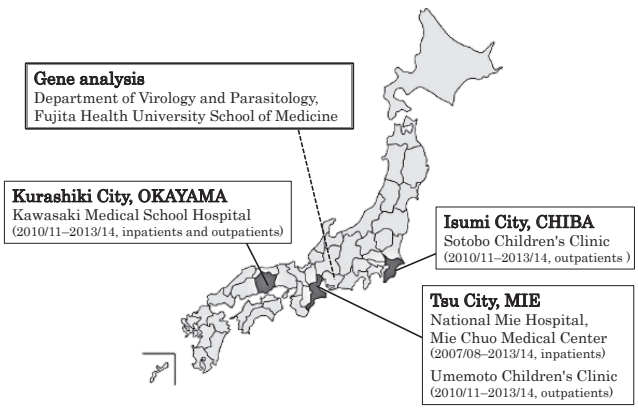

Fig. 1. Samples were collected from pediatric patients with rotavirus gastroenteritis who visited 6 institutions located in 3 areas of Japan.

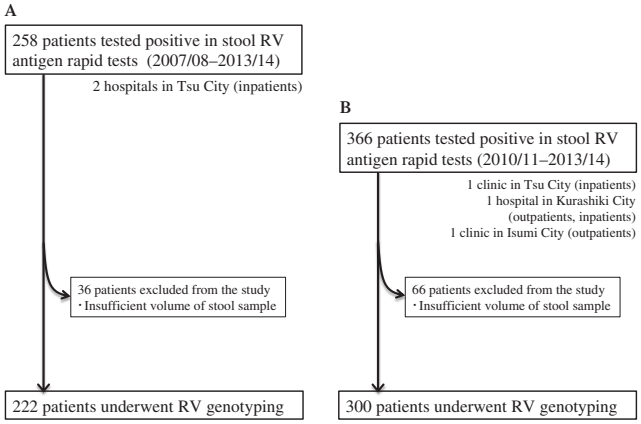

Fig. 2. Flow diagram for the selection of patients for rotavirus (RV) genotyping.

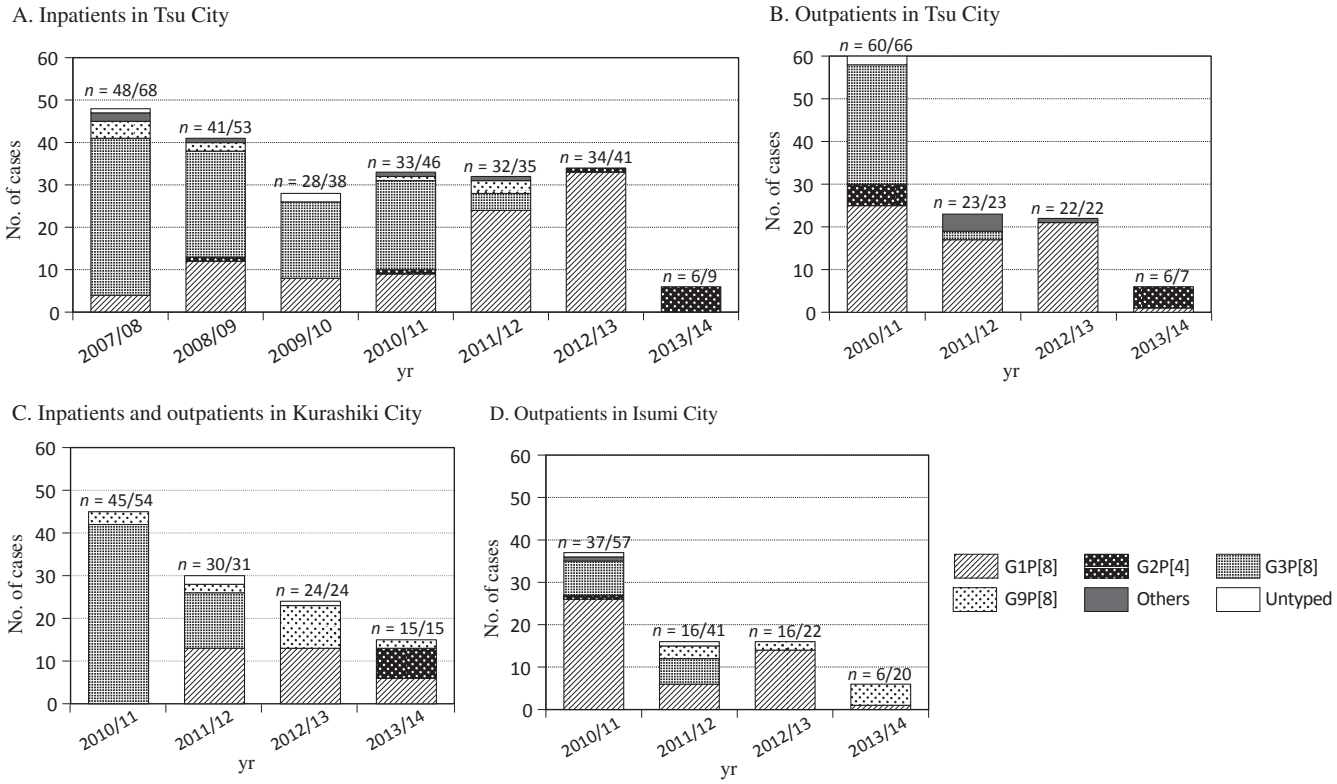

Fig. 3. Distribution of the genotype for each season and site. NOTE: *n* = the number of rotavirus (RV)-positive cases detected with the antigen rapid test / the number of RV-positive cases detected with polymerase chain reaction.

plification, the T32 primer was used along with G1, G2, G3, G4, G8, and G9 genotype-specific primers, to identify the G types. For P typing, a pair of primers, 5′–TGGCTTCGTTCATTTATAGACA–3′ and 5′–CTAAATGCTTTTGAATCATCCCA–3′, corresponding to the common sequences of the *VP4* gene, including nucleotides 11–32 and 1,072–1,094, respectively, was used for the first amplification; a mixture of primers specific to each of the variable regions: P[8], P[4], P[6], and P[9], along with a primer corresponding to nucleotides 11–32, was used for the second amplification. The PCR products were separated using agarose gel electrophoresis, and the G and P types were confirmed based on the extent of migration (12,13).

Vaccine coverage rate: Because the RV vaccine is not listed as a routine vaccine, we did not have a precise vaccine coverage rate for each study site. As a replacement, we used information of vaccine shipments and recollected amounts for the study sites to estimate the vaccine coverage rate. According to this information, our study sites had estimated coverage rates of approximately 30% in the 2011/12 season, 46% in the 2012/13 season, and 55% in the 2013/14 season, except for Isumi City, which instated a policy in April 2013 to cover all costs of the RV vaccine for their residents; thus, its coverage rate is considered to be nearly 100%.

Ethics statement: The study was approved in an ethical review conducted at National Mie Hospital and Kawasaki Medical School, and informed consent was obtained from the parents of all participants before execution of the study. The study, protocol, and management of personal information were in compliance with the Ethical Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare, drafted based on the principles set forth in the Declaration of Helsinki.

RESULTS

From the 2 hospitals in Tsu City, a total of 258 acute gastroenteritis patients had positive results of RV antigen rapid tests between the 2007/08 and 2013/14 seasons (Fig. 2A). Among these, 36 patients were excluded owing to insufficient stool sample volume. Thus, RV (G or P) genotyping was performed for 222 (86%) samples. At the other study sites, 366 patients had positive test results for RV between the 2010/11 and 2013/14 seasons (Fig. 2B), and 66 patients were excluded owing to insufficient stool sample volume. Thus, RV genotype testing was performed for 300 (82%) patients. The characteristics of patients whose stool sample underwent RV genotype testing were collected. For both groups, the number of samples collected per year decreased after introduction of the RV vaccine; however, the median age and proportion of male patients did not change after vaccine introduction (data not shown).

The distribution of genotype for each season and site are presented in Fig. 3. G3P[8] was the predominant (61.0–77.1%) genotype before vaccine introduction among inpatients in Tsu City. However, G3P[8] drastically decreased after vaccine introduction, and G1P[8] predominated (97.1%) in the 2012/13 season. Additionally, in the 2013/14 season, G2P[4] emerged, together with a decrease in the number of patients (Fig. 3A). For outpatient samples from Tsu City, G3P[8] and G1P[8] were the 2 main genotypes (46.7% and 41.7%, respectively) before vaccine introduction. However, G3P[8] decreased drastically in the 2012/13 season whereas G1P[8] increased (95.5%); G2P[4] emerged in the 2013/14 season, similar to the findings among inpatients (Fig. 3B).

In Kurashiki City, G3P[8] was predominant (93.3%)

Table 1. RV gastroenteritis in patients with a history of RV vaccination

No.	Season	Age (Mo)	Sex	Address (City)	Hospitalization	Dehydration[1)]	Type of vaccine	Time from the final vaccination to onset (days)	RV genotype
1	2012/13	9	M	Tsu	Yes	No	RV1	151	G1P[8]
2	2012/13	10	F	Tsu	No	No	RV1	193	G1P[8]
3	2012/13	7	M	Isumi	No	NA	RV5	85	G1P[8]
4	2013/14	9	M	Tsu	No	No	RV1	158	G2P[4]
6	2013/14	26	M	Tsu	Yes	No	RV1	728	G2P[4]
5	2013/14	28	M	Tsu	No	Yes	RV1	756	G2P[4]
7	2013/14	16	M	Kurashiki	Yes	No	RV1	394	G2P[4]
8	2013/14	12	F	Kurashiki	Yes	No	RV5	251	G9P[8]

[1)]: Dehydration suggests loss of more than 5% of body weight.
NA, not available; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

among both outpatients and inpatients before vaccine introduction but decreased drastically thereafter; G1P[8] and G9P[8] increased in the first season after vaccine introduction, followed by the emergence of G2P[4] in the 2013/14 season (Fig. 3C).

Among outpatients in Isumi City, G1P[8] was the dominant genotype (70.3%) before vaccine introduction. However, both G1P[8] and G3P[8] decreased after vaccine introduction, and G9P[8] predominated (83.3%) (Fig. 3D).

Since the introduction of the RV vaccine in November 2011, 8 of the 294 patients enrolled in the study had received an RV vaccine (Table 1). During the 2012/13 season, 2 patients who received the RV1 and one patient who received the RV5 contracted RV gastroenteritis at 151, 193, and 85 days after the last dose, respectively, all of which were G1P[8]. In the 2013/14 season, 4 patients who received the RV1 and one patient who received the RV5 contracted RV gastroenteritis at 158, 728, 756, 394, and 251 days after the last dose, respectively. The RV genotypes were G2P[4] among patients who received the RV1 and G9P[8] in those who received the RV5.

DISCUSSION

We reported the distribution of the RV genotypes before and after the introduction of the RV vaccine in Japan. Samples were collected from 3 different study sites. The genotype distribution was similar for both Tsu City and Kurashiki City, where G3P[8] was the dominant genotype before vaccine introduction but was overtaken by G1P[8] for 2 seasons and then by G2P[4]. However, in Kurashiki City only, G9P[8] was observed after introduction of the vaccine. In several studies, the rapid spread and predominance of unusual DS-1-like G1P[8] rotavirus were reported during 2011–2013 in various locations across Japan. The increase in G1P[8] strains after vaccine introduction in Tsu City and Kurashiki City may be related to an increase in this unusual strain (14–16). On the other hand, the genotype distribution was quite different in Isumi City. There, G1P[8] was the predominant genotype prior to vaccine introduction, and then G9P[8] became the main genotype in the 2013/14 season. Isumi City is the only area where RV vaccination is recommended and funded by the city government. Thus, the coverage rate of the vaccine was close to 100% during this period, which was much higher than in the other study areas. In addition, the RV5 was used at a much higher rate. Differences in the coverage rate and the kind of vaccine used may play important roles in the genotype distribution. One caveat, however, is that the main genotype in Isumi City differed from that at the other sites before introduction of the vaccine. Thus, we could not conclude that the change in genotype distribution was caused by the vaccine alone. For Tsu City, we were able to compare genotypes between inpatients and outpatients. The trend was very similar for both groups, implying that the genotype is not related to the severity of disease.

Marked changes in genotype prevalence following vaccine introduction have been observed in other countries. In Brazil, the predominance of G2P[4] after RV1 introduction has been reported (17). In the United States, the prevalence of G3P[8] increased after RV5 introduction (18). In Australia, G2P[4] and G3P[8] increased sharply in regions using RV1 and RV5 (19), respectively; however, these phenomena were temporary, and no increase in disease severity has been reported. It is difficult to determine the cause of these changes, but monitoring such changes is necessary to ensure the long-term safety of the RV vaccine.

In the present study, we found 8 infants with a history of RV vaccination before contracting RV gastroenteritis. The genotypes of RV in these patients were all G1P[8] in the 2012/13 season and G2P[4] for most of them in the 2013/14 season. Especially for patients with the G2P[4] genotype, all received the RV1 prior to the onset of gastroenteritis. Some studies have implied that the selection pressure of the vaccine may have caused this phenomenon (18); however, in our results, the genotype in the vaccinated patients matched the dominant circulating genotype in each season. However, Korea (where the RV5 and RV1 were approved in 2007 and 2008, respectively) experienced an outbreak of G2P[4] in 2013, 6 to 7 years after the introduction of RV vaccines. Forty-four patients infected with the G2P[4] strain were reported, including 9 and 5 patients with a history of RV1 and RV5 vaccination, respectively (20). Thus, continuous monitoring of genotypes from patients with and without vaccination is important.

In our study, all inpatients and outpatients with acute gastroenteritis were asked to bring a stool sample, to undergo testing for RV infection. However, some patients with RV gastroenteritis do not visit hospitals because infection is not apparent or their symptoms are mild. Even if these patients do visit a clinic, it is difficult to collect stool samples at the time of an outpatient visit. Thus, the changes in the number of RV-positive cases are unlike-

ly to reflect the true picture of an epidemic, especially among outpatients. Furthermore, because the number of our study sites was very limited, it is possible that other parts of Japan may have different distributions of RV genotypes. Therefore, we may see different distributions of RV genotype in Japan if more study sites around the country were included in future studies.

Normally, when evaluating vaccine efficacy and changes in genotypes, the types of vaccine used and vaccination rates in the population are considered essential information. Because the RV vaccine is still not recommended as a routine vaccine in Japan, the precise vaccination coverage rate and the type of vaccine used are unclear. We estimated the vaccine coverage rate of the studied areas based on vaccine shipment and recollected vaccine information. This is our best estimate at the moment, and the estimated vaccine coverage rate is around 30–46%, except for in Isumi City (which is nearly 100%).

Nevertheless, despite the abovementioned limitation, it is still safe to say that after introduction of the RV vaccine, the circulating genotypes of RV have changed in Japan. We may observe more definite changes once the vaccination coverage rises and more cases with a vaccine history can be studied. Hence, continuous monitoring of the RV genotypes is of great importance.

In conclusion, this study presented the changes in RV genotypes distribution after RV vaccine introduction in Japan. However, it is difficult to evaluate whether these changes were owing to the effect of vaccination or represented natural epidemiological changes. Long-term monitoring of the RV genotypes is necessary.

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