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Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life

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ABSTRACT

A phase III, randomized, double-blind study evaluated the efficacy, reactogenicity, safety and immunogenicity of a human rotavirus vaccine, RIX4414 in Japanese infants aged 6–14 weeks when administered as two doses (0, 1-month schedule). Efficacy against any and severe rotavirus gastroenteritis leading to medical intervention caused by circulating wild-type rotavirus from two weeks post-Dose 2 until two years of age was 79.3% (95% CI: 60.5–89.8%) and 91.6% (95% CI: 62.4–99.1%), respectively. Solicited, unsolicited symptoms and serious adverse events were reported at a similar frequency in both groups. Serum anti-rotavirus antibody seroconversion rate one-month post-Dose 2 was 85.3% (95% CI: 68.9–95%) in RIXX4414 group. RIX4414 was efficacious, well-tolerated and immunogenic in Japanese infants and introduction of vaccination could help in reducing the disease burden.

1. Introduction

Rotavirus is the single main cause of severe acute gastroenteritis in children less than five years of age, resulting in over 527,000 deaths worldwide annually [1]. The majority of rotavirus-related deaths are seen in developing countries; nevertheless, the disease is not restricted to poor settings. Although rotavirus deaths are seldom observed in developed countries, rotavirus continues to be the main cause of gastroenteritis-related hospitalizations and doctor visits [2,3].

In a prospective surveillance in Japan, rotavirus was detected in approximately 58% of gastroenteritis hospitalizations in children less than five years of age [4]. Further, in a retrospective surveillance in Japan, 39–44% of year-round hospitalization in children aged <5 years with gastroenteritis was due to rotavirus, indicating rotavirus as the most important etiological agent of acute gastroenteritis [5]. A ten-year rotavirus hospitalization survey in Japan (between 1987 and 1996) reported the highest rate of rotavirus hospitalization incidence of 42.2 per 1000 person years in the 6–11 months age group in the overall time period studied [6]. Rotavirus gastroenteritis was also estimated to result in approximately 800,000 doctor visits every year leading to medical intervention among children aged 0–5 years in Japan [7]. At present, the treatment of rotavirus gastroenteritis is limited to symptomatic measures and no antiviral therapy is available.

A live-attenuated human rotavirus vaccine RIX4414 (*Rotarix*™, GlaxoSmithKline Biologicals) contains the most common G1P[8] strain which was derived from the parent 89-12 strain [8,9]. Clinical trials conducted across Europe, Latin America, Asia with the human rotavirus vaccine have demonstrated high efficacy against severe rotavirus gastroenteritis caused by circulating wild-type rotavirus [10–12]. Further, rotavirus vaccination also significantly reduced the incidence of severe rotavirus gastroenteritis among African

Abbreviations: AE, adverse event; ATP, according-to-protocol; CCID, Cell Culture Infective Dose; CI, confidence interval; DTPa, diphtheria-tetanus-acellular pertussis; ELISA, Enzyme-Linked Immunosorbent Assay; GMC, geometric mean concentration; GSK, GlaxoSmithKline; HBV, hepatitis B vaccine; MedDRA, Medical Dictionary for Regulatory Activities; RT-PCR, reverse transcriptase-polymerase chain reaction; SAE, serious adverse event; TVC, total vaccinated cohort; WT, wild-type.

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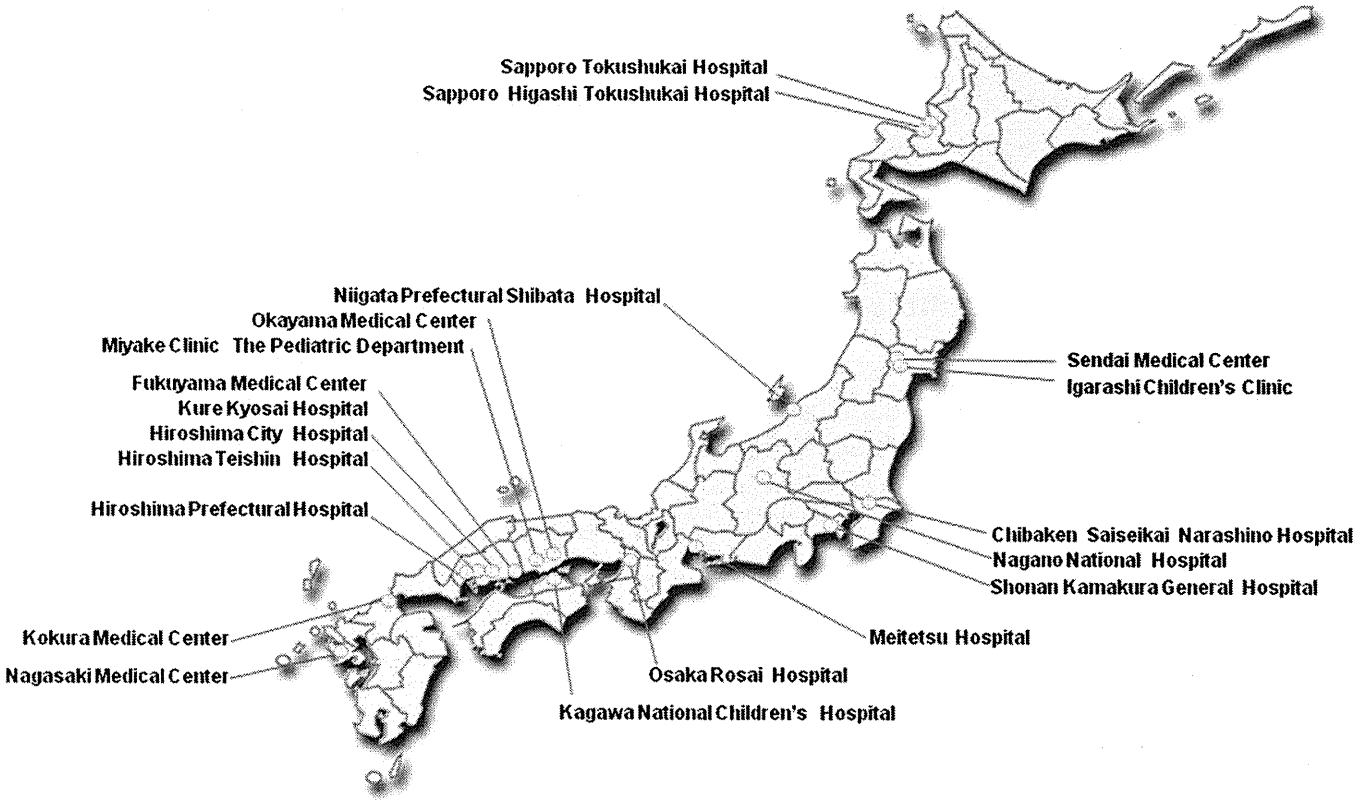

Fig. 1. Study site map.

infants [13]. The safety of the RIX4414 vaccine has also been proved in a large trial with over 63,000 infants [14].

This study, conducted in Japan assessed the efficacy, immunogenicity and safety of RIX4414 vaccine when administered to Japanese infants aged 6–14 weeks.

2. Materials and methods

2.1. Study design and population

This phase III, randomized (vaccine: placebo = 2:1 ratio), double-blind, placebo-controlled study was conducted across 20 study centers (two primary emergency care and 18 secondary emergency care centers) essentially covering the whole of Japan, with Hokkaido in the North, mainland, Kyoshu and Shikoku in the South (107625/NCT00480324) between June 2007 and November 2009 (Fig. 1). Of the 20 centers, 12 were public hospitals and eight were private hospitals. Parents/guardians of children who received care at the participating centers were approached to seek their willingness to let their child/ward participate in the study. Parents/guardians of eligible study participants signed the written informed consent before performance of any study-related procedures. The study protocol, amendment and informed consent were reviewed and approved by the ethics committee prior to study initiation. The study was conducted following Good Clinical Practice, including the Declaration of Helsinki. Ethical approval was sought from the Institutional Review Board of each study centers.

Two oral doses of RIX4414 vaccine/placebo were administered to healthy infants 6–14 weeks of age at Dose 1 according to 0, 1 month vaccination schedule. The routine childhood vaccines (diphtheria-tetanus-acellular pertussis [DTPa] and hepatitis B vaccine [HBV]) recommended in Japan was allowed to be administered concomitantly with the study vaccines according to local immunization practice. Infants were excluded if they had received any investigational drug or vaccine 30 days preceding the first dose of study vaccine/placebo, received other rotavirus vaccine, were administered immunosuppressive drugs, had a history of chronic gastrointestinal disease, suspected immunosuppression or immunodeficiency or had gastroenteritis seven days preceding the administration of first vaccine dose. Vaccination was postponed in case of an acute febrile illness, vomiting or diarrhea at the time of scheduled vaccination. Allergy to the study vaccine or any other component of the study vaccine and the presence of uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract established absolute contraindication to vaccination.

2.2. Study vaccines

Each dose (1 ml) of the lyophilized RIX4414 vaccine (*Rotarix*™) contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of live attenuated human rotavirus RIX4414 strain. The composition of placebo was similar to that of the RIX4414 vaccine but without the vaccine strain and was identical in appearance to the vaccine. The lyophilized vaccine and placebo were reconstituted with the supplied buffer before oral administration.

2.3. Assessment of efficacy

Occurrence of gastroenteritis (diarrhea [≥3 looser than normal stools per day] with or without vomiting) that led to medical intervention was actively followed-up from Dose 1 until two years of age. Starting from Day seven after Dose 1, the parents/guardians of children were contacted at least once every two weeks to check for the occurrence of gastroenteritis episodes. They were contacted either through telephone, short messaging services of the mobile

phone or other convenient means of communication repeatedly to facilitate hospital visits in case their infants had gastroenteritis. The parents/guardians were also advised to contact the study staff actively in case of occurrence of gastroenteritis in their child. During each gastroenteritis episode leading to medical intervention (defined as medical doctor visit, an emergency room visit or hospitalization), the parents/guardians were also advised to fill in a diary card for gastroenteritis episode and return it to the investigators. The investigators transcribed information regarding the number and duration of diarrhea and vomiting episodes, fever and the treatment provided from the diary card into the case report forms. Based on this information, statisticians assessed the intensity of each gastroenteritis episode using a 20-point Vesikari scale. In this scale, an episode of gastroenteritis with a score of ≥11 was considered severe [15].

2.3.1. Assessment of gastroenteritis episodes

Parents/guardians of children were advised to collect stool samples as soon as possible (no later than seven days after the commencement of gastroenteritis episode) during each gastroenteritis episode that occurred throughout the study period. Two occurrences of gastroenteritis were considered as two separate episodes if there were more than five diarrhea-free days between the episodes. The gastroenteritis stool samples were tested for rotavirus using Enzyme-Linked Immunosorbent Assay (ELISA) at GSK Biologicals. Rotavirus positive stool samples were tested further using reverse transcriptase-polymerase chain reaction (RT-PCR) followed by reverse hybridization for determining the G (VP7) and P (VP4) types [16]. This method permits differentiation between the wild-type G1 rotavirus and the vaccine virus.

2.4. Assessment of safety and reactogenicity

The investigator was responsible to document the AEs or SAEs in the patient case report form. The investigators used their medical judgment while diagnosing the AEs/SAEs and establishing causality with the study vaccine.

Occurrence of solicited AEs (fever, irritability, diarrhea, vomiting, loss of appetite, cough/runny nose) was recorded in diary cards by the parents/guardians during the eight-day post-vaccination follow-up period. The intensity of each of these events was assessed by the investigator based on a 4-point scale where Grade 0 indicated normal and Grade 3 indicated severe. Solicited AEs of Grade 3 intensity were defined as follows: ≥6 looser than normal stools per day (diarrhea), ≥3 episodes of vomiting per day (vomiting), axillary temperature >39 °C (fever), prevented or interfered with normal daily activities (cough/runny nose, irritability, loss of appetite).

Unsolicited AEs were recorded during the 31-day post-vaccination follow-up period after each dose. The intensity of these symptoms was also graded by the investigator, where Grade 1 indicated mild and Grade 3 indicated severe symptoms.

SAEs were recorded throughout the study period.

2.5. Assessment of immunogenicity

Blood samples for immunogenicity assessment were collected from a subset of 54 infants whose parents/guardians consented for withdrawal of blood samples from their wards. After obtaining consent, blood samples were collected from this subset at pre-vaccination and one month post-Dose 2 of RIX4414 vaccine/placebo. The samples were tested using ELISA at GSK Biologicals laboratory to measure the anti-rotavirus IgA antibody concentration. The assay cut-off was 20 U/ml [8,17].

2.6. Statistical analyses

All statistical analysis was performed using SAS 9.1 and 95% confidence interval (CI) calculated using Proc StatXact-7.

A standard SAS® program was used to generate a randomization list to number the vaccine. A 2:1 block randomization ensured balance between the two treatment arms – a unique treatment number identified the vaccine that had to be administered to the same infant. The treatment allocation at each study site was performed using the central randomization system on the Internet (SBIR). The randomization algorithm used a minimization procedure to account for each center. Blinding was maintained throughout the study. The study investigators, study personnel and the parents/guardians of infants were not aware of the study vaccine administered.

A sample size of 765 infants were planned to be enrolled to have 612 evaluable infants considering 20% of infants may not be evaluable for the primary objective. Assuming an attack rate of 8% in the placebo group for rotavirus gastroenteritis leading to medical intervention from 2 weeks after Dose 2 up to two years of age, an efficacy value of 80% would provide the study 92% power to have a lower limit of the 95% CI on vaccine efficacy ≥10%.

Final analysis was triggered when 28 rotavirus gastroenteritis cases caused by the circulating wild-type rotavirus leading to medical intervention were reported during the efficacy follow-up period. An annex analysis was done when all the infants completed their last visit at the end of two years of age (study was blinded till the end). In this paper, we present the results of the analysis that was done after study completion (i.e. efficacy/safety follow-up up to two years of age).

The efficacy analysis on primary endpoint was done on the according-to-protocol (ATP) cohort. The ATP cohort for efficacy included infants who had completed the two-dose vaccination course of RIX4414 vaccine/placebo, had entered the efficacy surveillance period starting from two weeks post-Dose 2, had no rotavirus in their gastroenteritis stool samples other than the vaccine strain between the day of Dose 1 and two weeks after Dose 2 of the study vaccine/placebo and those who complied with the protocol. The efficacy analysis was undertaken from two weeks post-Dose 2 of RIX4414 vaccine/placebo until two years of age. For the efficacy analysis, gastroenteritis episodes with circulating wild-type rotavirus (other than the vaccine strain) identified was considered.

The 95% CI was calculated for vaccine efficacy against any rotavirus gastroenteritis leading to medical intervention during the defined efficacy period (primary endpoint). Similar 95% CI calculations were performed for efficacy against severe rotavirus gastroenteritis, any and severe rotavirus gastroenteritis caused by circulating G1 and non-G1 types and against hospitalizations due to rotavirus gastroenteritis (secondary endpoints). The number of any and severe rotavirus gastroenteritis episodes leading to medical intervention prevented by vaccination were obtained by calculating 100 times the difference in the incidence rate between the RIX4414 and placebo groups. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [18].

Analysis of safety and reactogenicity was performed on the total vaccinated cohort (TVC). This cohort included all infants with at least one study vaccine administration documented. The overall incidence of solicited and unsolicited AEs with 95% CI were tabulated for the eight-day and 31-day post-vaccination follow-up period, respectively. The incidence of each individual solicited AE was calculated per group with 95% CI. The percentage of infants with unsolicited AEs and SAEs classified based on Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by group with 95% CI.

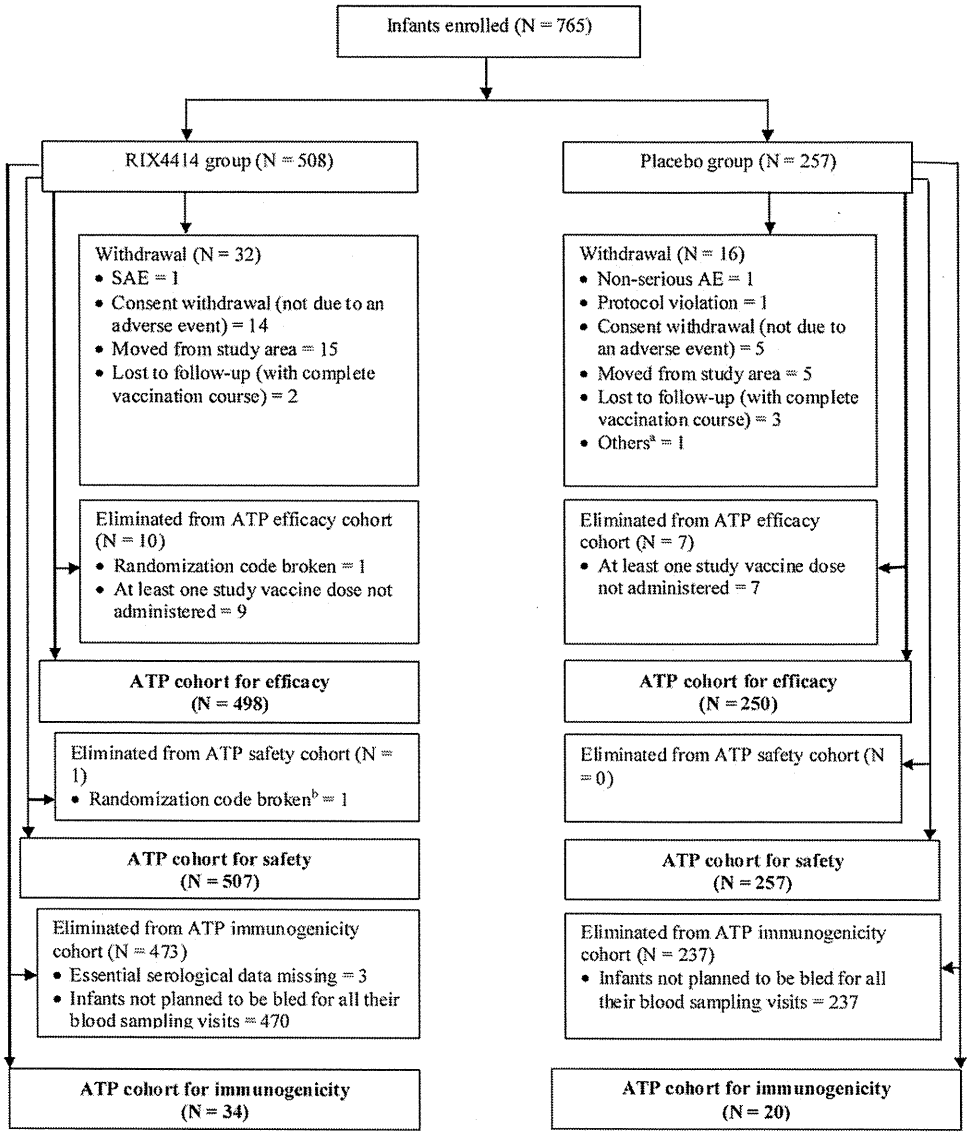

Fig. 2. Trial profile. *Notes*: (a) Others: subject's mother's pregnancy. (b) Randomization code was broken because the infant developed an SAE (hepatobiliary disorder) 20 days after Dose 2 of RIX4414. The investigator initially considered this SAE to be causally related to vaccination. However, further investigation of the SAE after unblinding revealed that the SAE was unrelated to vaccination.

Immunogenicity analysis was performed on the ATP cohort for immunogenicity comprising infants who had received the two doses of RIX4414 vaccine/placebo, complied with the protocol and for whom pre- and post-vaccination immunogenicity data was available. The anti-rotavirus IgA antibody seroconversion rates (anti-rotavirus IgA antibody concentration ≥20 U/ml in initially seronegative infants) and geometric mean concentrations (GMCs) were calculated with 95% CI one month post-Dose 2 in the subset of 54 infants.

3. Results

3.1. Study participants and demography (Total vaccinated cohort)

A total of 765 infants were enrolled; 749 completed two doses of RIX4414 vaccine/placebo and 717 infants completed the efficacy follow-up until two years of age. The trial profile with reasons for withdrawal has been provided in Fig. 2. The mean age of infants at Dose 1 of RIX4414 vaccine/placebo was 7.7 ± 2.01 weeks and at Dose 2 was 12.7 ± 2.08 weeks. The proportion of males and females in both groups were similar and all infants were of Japanese origin. In this study, routine childhood vaccines administered up to one month post-Dose 2 of RIX4414/placebo were recorded. About 3% (23/765) and 4.3% (32/765) of infants received routine vaccination concomitantly with Dose 1 and Dose 2 of the study vaccine, respectively. Only two infants (0.3%; 2/749) received oral poliovirus vaccine concomitantly. The percentage infants who received routine vaccination between Dose 1and Dose 2, excluding the vaccinations given concomitantly with RIX4414/placebo was 3.5% (27/765); between Dose 2 and one month post-Dose 2 was 40.7% (305/749).

3.2. Efficacy afforded by the vaccine (ATP cohort for efficacy)

During the efficacy follow-up period from 2 weeks post Dose 2 up to two years of age (mean duration: 1.68 years in RIX4414 and 1.67 years in placebo groups), the percentage of infants with at least one gastroenteritis episode leading to medical intervention was more in the placebo group ($N = 111$; 44.4%) when compared to the RIX4414 group ($N = 201$; 40.4%).

From two weeks post-Dose 2 up to two years of age, there were 34 rotavirus gastroenteritis episodes reported in the placebo group

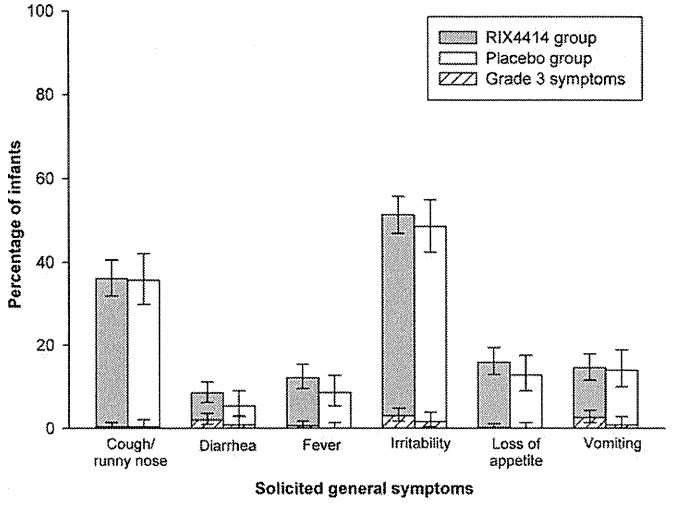

Fig. 3. Solicited general symptoms reported during the eight-day post-vaccination follow-up period (total vaccination cohort).

(13.6%) when compared to 14 episodes in RIX4414 group (2.8%) resulting in a vaccine efficacy of 79.3% (95% CI: 60.5–89.8%) against the primary outcome of any rotavirus gastroenteritis caused by circulating wild-type rotavirus that led to medical intervention ($p < 0.001$) (Table 1). Vaccination with RIX4414 prevented 7 any rotavirus gastroenteritis episodes leading to medical intervention per 100 vaccinated infant per year in the first two years of life (Table 2).

There were two severe rotavirus gastroenteritis episodes reported in the RIX4414 group (0.4%) and 12 episodes in the placebo group (4.8%). A vaccine efficacy of 91.6% (95% CI: 62.4–99.1%) was observed against severe rotavirus gastroenteritis leading to medical intervention. Vaccination with RIX4414 prevented 2.7 severe rotavirus gastroenteritis episodes leading to medical intervention per 100 vaccinated infant per year in the first two years of life (Table 2).

G1 wild type (17 any rotavirus gastroenteritis and 7 severe rotavirus gastroenteritis) and G3 (16 any rotavirus gastroenteritis and 4 severe rotavirus gastroenteritis) were the most common G-types detected during the study period (June 2007–November 2009); P[8] wild type (45 any rotavirus gastroenteritis and 14 severe rotavirus gastroenteritis) was the dominant P-type detected during the same time period. All the G3 isolates reported in this study were G3P[8]. Vaccine efficacy against the G and P rotavirus types is provided (Table 1).

3.3. Reactogenicity and safety (Total vaccinated cohort)

During the eight-day post-vaccination follow-up period, AEs (solicited and unsolicited) occurred at a similar frequency in both RIX4414 (75.8% [95% CI: 71.8–79.5%]) and placebo (73.5% [95% CI: 67.7–78.8%]) groups. Irritability (any and Grade 3) was the most common solicited general AE reported in both groups during the eight-day follow-up period (Fig. 3).

At least one unsolicited AE was recorded in 279 infants (54.9% [95% CI: 50.5–59.3%]) from the RIX4414 group and 144 infants (56.0% [95% CI: 49.7–62.2%]) from the placebo group during the 31-day post-vaccination follow-up period. Eczema (14.2% in RIX4414 and 11.3% in placebo) and upper respiratory tract infection (9.8% in RIX4414 and 9.7% in placebo) were the most common unsolicited AE reported in both groups.

At least one SAE was recorded in 72 infants (14.2% [95% CI: 11.3–17.5%]) in the RIX4414 group and 44 infants (17.1% [95% CI: 12.7–22.3%]) in the placebo group. During the entire study period, there were no fatal events reported. None of the SAEs recorded was causally related to vaccination. No intussusception case was reported.

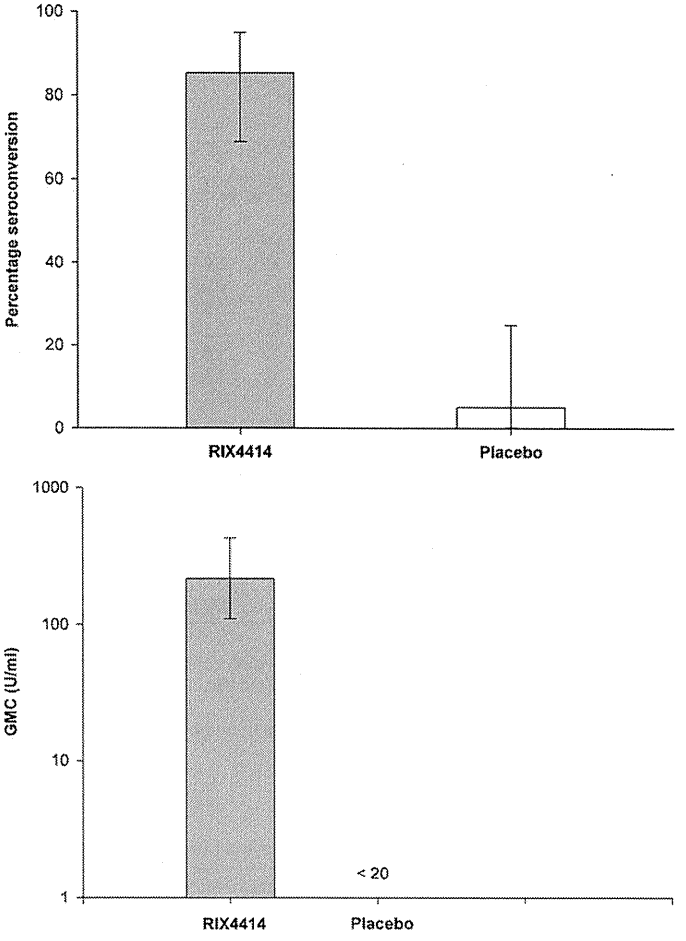

Fig. 4. Anti-rotavirus seroconversion rate and overall geometric mean concentrations at one month post-Dose 2 (ATP immunogenicity cohort).

3.4. Immunogenicity (ATP cohort for immunogenicity)

Serum anti-rotavirus IgA response was assessed in a subset of 54 infants (34 in RIX4414 and 20 in placebo). One month post-Dose 2 of RIX4414 vaccine/placebo, the anti-rotavirus IgA seroconversion rate was 85.3% (95% CI: 68.9–95%) in the RIX4414 group and 5% (95% CI: 0.1–24.9%) in the placebo group. Overall GMCs were 217 U/mL (95% CI: 109.9–428.6) in the RIX4414 group and <20 U/mL in the placebo group (Fig. 4).

4. Discussion

This was the first study conducted to evaluate the efficacy, safety and immunogenicity of two doses of a live-attenuated human rotavirus vaccine, RIX4414, in Japanese infants. During the first two years of life, RIX4414 vaccine provided protection against any and severe rotavirus gastroenteritis requiring medical intervention with a vaccine efficacy of 79.3% (95% CI: 60.5–89.8%) and 91.6% (95% CI: 62.4–99.1%), respectively. These results are similar to that observed in a two-year efficacy study in Europe where efficacy against any rotavirus gastroenteritis was 78.9% and against severe rotavirus gastroenteritis was 90.4% [10]. Furthermore, vaccination with RIX4414 resulted in the prevention of 7 any rotavirus gastroenteritis episodes and approximately 3 severe rotavirus gastroenteritis episodes leading to medical intervention

Table 1
Efficacy of RIX4414 against any and severe rotavirus gastroenteritis, any and severe rotavirus gastroenteritis caused by G1 and non-G1 types and rotavirus gastroenteritis-related hospitalization from two weeks post-Dose 2 up to two years of age (ATP cohort for efficacy).

Type of gastroenteritis	RIX4414 N^a = 498		Placebo N^a = 250		Vaccine efficacy % (95% CI)	p-Value[e]
	n^b	%[c] (95% CI)[d]	n^b	%[c] (95% CI)[d]		
Any rotavirus gastroenteritis leading to medical intervention						
Overall	14	2.8 (1.5–4.7)	34	13.6 (9.6–18.5)	79.3 (60.5–89.8)	<0.001
By rotavirus type						
G1WT[f]	4	0.8 (0.2–2.0)	13	5.2 (2.8–8.7)	84.6 (50.0–96.3)	<0.001
G2	1	0.2 (0.0–1.1)	2	0.8 (0.1–2.9)	74.9 (−382.2 to 99.6)	0.521
G3[g]	3	0.6 (0.1–1.8)	13	5.2 (2.8–8.7)	88.4 (57.8–97.9)	<0.001
G4	1	0.2 (0.0–1.1)	1	0.4 (0.0–2.2)	49.8 (-3840.6–99.4)	1.000
G9	5	1.0 (0.3–2.3)	5	2.0 (0.7–4.6)	49.8 (−118.1 to 88.4)	0.430
P8WT[f]	13	2.6 (1.4–4.4)	32	12.8 (8.9–17.6)	79.6 (60.1–90.2)	<0.001
P4	1	0.2 (0.0–1.1)	2	0.8 (0.1–2.9)	74.9 (−382.2 to 99.6)	0.521
Severe rotavirus gastroenteritis leading to medical intervention						
Overall	2	0.4 (0.0–1.4)	12	4.8 (2.5–8.2)	91.6 (62.4–99.1)	<0.001
By rotavirus type						
G1WT[f]	1	0.2 (0.0–1.1)	6	2.4 (0.9–5.2)	91.6 (31.0–99.8)	0.014
G3	0	0.0 (0.0–0.7)	4	1.6 (0.4–4.0)	100.0 (24.0–100.0)	0.025
G9	1	0.2 (0.0–1.1)	2	0.8 (0.1–2.9)	74.9 (−382.2 to 99.6)	0.521
P8WT[f]	2	0.4 (0.0–1.4)	12	4.8 (2.5–8.2)	91.6 (62.4–99.1)	<0.001
Rotavirus gastroenteritis-related hospitalization						
	1	0.2 (0.0–1.1)	2	0.8 (0.1–2.9)	74.9 (−382.2 to 99.6)	0.521

[a] N = number of infants included in each group.
[b] n = number of infants reporting at least one event.
[c] % = percentage of infants reporting at least one event.
[d] 95% CI = 95% confidence interval.
[e] p-Value = two sided exact p-value conditional to number of cases.
[f] WT = wild-type.
[g] All G3 isolates were G3P[8].

Table 2
Risk difference per 100 infant per year during the first two years of life (ATP cohort for efficacy).

	Type of gastroenteritis	RIX4414 N^a = 498			Placebo N^a = 250			Rate difference per 100 infants per year (95% CI)[d]
		n^b	Incidence rate (episodes per 100 infants per year)	95% CI[c]	n^b	Incidence rate (episodes per 100 infants per year)	95% CI[c]	
Any rotavirus gastroenteritis leading to medical intervention	First year of life	5	1.4	0.6–3.4	12	7.0	4.0–12.4	5.6 (2.0–11.0)
	Two years of life	14	1.7	1.0–2.9	34	8.7	6.2–12.1	7.0 (4.2–10.5)
Severe rotavirus gastroenteritis leading to medical intervention	First year of life	1	0.3	0.0–2.0	4	2.3	0.9–6.1	2.0 (−0.2 to 5.8)
	Two years of life	2	0.2	0.1–1.0	12	2.9	1.7–5.2	2.7 (1.2–4.9)

[a] N = number of infants in each group.
[b] n = number of infants reporting at least one event.
[c] 95% CI = 95% confidence interval.
[d] Risk difference = incidence rate in placebo − incidence rate in RIX4414.

per 100 vaccinated infants years in the first two years of life. Considering that infection with rotavirus results in approximately 800,000 doctor visits per year in Japan [7], prevention of any and severe rotavirus gastroenteritis episodes could help in drastically reducing the hospital visits for children <5 years of age in the country.

One interesting aspect of rotaviruses is that the rotavirus types circulating differ substantially from year to year. Therefore, it is very important to evaluate if the rotavirus vaccine provides an overall protection against rotavirus gastroenteritis caused by the circulating rotavirus types which could eventually help in reducing the disease burden. In the present study (between June 2007 and November 2009), G1 wild type and G3 were the predominant rotavirus types circulating during the study period. Since, RIX4414 vaccine contains the G1 type, it was not surprising that the vaccine provided high protection against any and severe rotavirus gastroenteritis leading to medical intervention caused by G1 rotavirus type. Interestingly, RIX4414 vaccine provided protection against any and severe rotavirus gastroenteritis caused by circulating G3 type. However, the G3 isolates in this study were all associated with P[8] to form the G3P[8] strain. Currently the mechanism of heterotypic protection is unclear and thus cross reactive epitopes on the VP4 protein may aid in the heterotypic protection offered by G type. Due to the low circulation of other non-vaccine G types, efficacy against these types could not be established. However, heterotypic vaccine efficacy against severe rotavirus gastroenteritis caused by these rotavirus types (i.e. G2 [vaccine efficacy = 85.5%], G4 [vaccine efficacy = 95.4%] and G9 [vaccine efficacy = 85%]) during the first two years of life has been established in an earlier study conducted elsewhere [10].

Reactogenicity and safety results showed that the vaccine was well tolerated with similar frequencies of solicited general AEs reported in both groups. Irritability was the most common solicited general AE reported (any and grade 3), which is in line with that reported in a recent integrated safety analysis [19]. There were no fatal events in this study, the occurrence of unsolicited AEs and the SAEs were similar in both groups.

In industrialized countries like Japan, the deaths associated with rotavirus gastroenteritis are very rare. However, rotavirus gastroenteritis results in considerable number of doctor visits (800,000

doctor visit per year) and hospitalizations thereby increasing the overall direct cost to the country. The mean direct medical cost of rotavirus hospitalization is approximately 136,000 Yen per hospital admission [4]. Extrapolation of this data to the annual rotavirus hospitalization incidence of 78,000 in Japanese children (<5 years of age) would result in a staggering direct medical cost of 10 billion Yen [4]. The number of any and severe rotavirus gastroenteritis cases leading to medical intervention prevented when put together would ensue in significant cost savings to the country in the long run.

Although, introduction of rotavirus vaccination may not have an immediate visible affect as observed in developing countries, vaccination would indeed reduce the rate of hospitalization and doctor visits due to rotavirus gastroenteritis eventually. This was evidenced in a study conducted in the United States, where there was a drastic reduction in the rate of hospitalizations (in the range of 16–45% between years 2007 and 2008) after the introduction of rotavirus vaccine when compared to the pre-rotavirus vaccination period [20]. A similar reduction in rotavirus-related hospitalization could be expected in Japan as well.

5. Conclusions

Two oral doses of the RIX4414 vaccine was found to be highly efficacious against any and severe rotavirus gastroenteritis caused by circulating G1 and non-G1 rotavirus types leading to medical intervention in Japanese infants in the first two years of life. These data support vaccination as a primary tool in reducing the rotavirus gastroenteritis hospitalization and gastroenteritis-related doctor visits in Japan. Introduction of the vaccine into the immunization program in Japan is expected to be beneficial in reducing the rotavirus disease burden in Japanese infants.

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Original Article

Cost-Effectiveness Analysis of a Universal Rotavirus Immunization Program in Japan

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SUMMARY: In anticipation of the imminent licensure of rotavirus vaccine, we evaluated the cost-effectiveness of rotavirus vaccine in Japan by taking into account the considerable variations in the incidence of rotavirus-associated hospitalizations previously reported in the literature. We assumed that the variation was due to local differences in healthcare utilization practices rather than a true difference in the incidence of severe rotavirus gastroenteritis. Thus, a Markov model was constructed such that the sum of rotavirus-associated hospitalizations and outpatient visits was set a constant value of 129 cases per 1,000 child-years. We calculated the direct medical cost, the indirect cost, and the quality-adjusted life year (QALY) loss in children aged less than 5 years. For the base case scenario, the incremental cost-effectiveness ratio (ICER) per QALY gained was ¥9.8 million from the healthcare perspective, but it was ¥900,000 from the societal perspective, making the program of universal immunization against rotavirus highly cost-effective. Furthermore, the universal immunization program was found to be cost-effective from the societal perspective for any of the previously reported incidence rates of rotavirus-associated hospitalization. Thus, the introduction of the rotavirus vaccine into the childhood immunization schedule and its co-administration with other childhood vaccines will be a cost-effective public health intervention in Japan.

INTRODUCTION

Rotavirus is the major cause of severe, dehydrating diarrhea, causing an estimated 611,000 deaths annually among children aged less than 5 years in developing countries (1). The mortality due to rotavirus in high-income countries is much lesser, accounting for a median of 44% of diarrheal hospitalizations among children less than 5 years of age in these countries (1). After the successful large phase III efficacy and safety trials (2,3), two, live oral rotavirus vaccines, RotaTeq (Merck & Co., Whitehouse Station, N.J, USA) and Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), have been licensed in more than 100 countries and have been incorporated into the routine childhood immunization programs of more than 20 countries (4). A substantial reduction in the number of cases of rotavirus gastroenteritis has already been observed in countries where the vaccine was included in the routine childhood immunization program (5,6).

In Japan, an estimated 800,000 children aged less than 6 years visited pediatric clinics and the outpatient department of hospitals annually for the treatment of rotavirus gastroenteritis (7). In addition, each year, approximately 78,000 cases of rotavirus-associated hospitalizations were reported among children aged less than 5 years (8). Despite the substantial burden of rotavirus gastroenteritis, neither rotavirus vaccine was licensed at the time of preparation of this manuscript. Anticipating the imminent licensure of Rotarix and RotaTeq vaccines, which were filed for approval in 2009 and 2010 (9,10), respectively, we carried out a cost-effectiveness analysis of rotavirus vaccination, with the view to facilitate the decision of whether rotavirus vaccination should be included in the universal immunization program in Japan. Previous studies have shown that the incidence of rotavirus-associated hospitalization is one of the most influential parameters that affect the cost-effectiveness of rotavirus vaccination (11). However, the estimate of the incidence of rotavirus-associated hospitalizations among Japanese children aged less than 5 years varies considerably: 3.8 and 4.9 per 1,000 child-years in Tsu city and Ise city, Mie Prefecture (12) and 13.2 per 1,000 child-years in Honjo city, Akita Prefecture (8). We, therefore, considered it important to examine the economic impact of rotavirus vaccination at varying incidences of rotavirus-associated hospitalizations.

METHODS

We evaluated the potential impact of rotavirus vaccination on the direct medical costs, indirect costs, and the quality of life associated with rotavirus-associated hospitalizations and outpatient visits in children aged less than 5 years in Japan. The incremental cost-effectiveness ratio (ICER) was defined as the ratio of the incremental cost over the incremental quality-adjusted life years (QALY) gained by the universal rotavirus immunization program. The immunization program was

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evaluated from the perspectives of the healthcare system and of the society.

Model structure: A Markov model was constructed for a hypothetical 2009 birth cohort of 1.1 million Japanese children (13) who were followed up for 5 years, and the number of rotavirus-associated hospitalizations and outpatient visits in this cohort was calculated for 2 different scenarios: absence of rotavirus immunization program and the implementation of a universal rotavirus immunization program. The health states of the children in the cohort were determined according to the previous health states and probabilities, which were related to rotavirus-associated hospitalization and outpatient visits and the vaccine efficacy. We developed a computer program in the Perl language to perform the calculations. The Markov model used in this study has been previously described in detail (14). On the basis of the outcome of the model, we calculated the direct medical cost, the indirect cost, and the QALY loss in the cohort using Microsoft Excel 2007.

Incidence of rotavirus gastroenteritis: The national incidence of rotavirus-associated hospitalizations was estimated at 6 hospitalizations per 1,000 child-years by pooling the average number of rotavirus-associated hospitalizations per year and the total population estimated for the 3 abovementioned locations in Japan (8,12). Considering the national incidence and an average age distribution of the 3 estimates, the age-specific number of rotavirus-associated hospitalizations was calculated on the basis of the probability of rotavirus-associated hospitalization (Table 1).

An incidence of 123 outpatient visits due to rotavirus gastroenteritis per 1,000 child-years was applied to the model birth cohort: half the number of outpatient visits for the ages of 4 years and 5 years, as reported in a rotavirus disease burden study (7), was assigned to the number of visit for the age of 4 years, and the incidence was calculated by adjustment for the 2009 birth cohort (13). We also assumed that the age distribution of rotavirus-associated outpatient visits was equivalent to that of rotavirus-associated hospitalizations (Table 1).

Costs associated with rotavirus gastroenteritis: The direct medical cost and the indirect cost of rotavirus-associated hospitalizations and outpatient visits are summarized in Table 2. All costs were inflated to the 2009 Japanese yen using the general and medical components of the consumer price index (15). The direct medical cost per rotavirus-associated outpatient visit was assumed to be ¥13,830, which is one-tenth of the direct medical cost of ¥138,298 per rotavirus-associated hospitalization (8,16). The loss of productivity of the caregivers was calculated as the indirect cost associated with rotavirus gastroenteritis. We assumed that caregivers missed 5 and 2 days of work for the duration of hospitalization and outpatient department visits, respectively (8,16). The productivity loss per caregiver was

Table 1. Probability of rotavirus hospitalization

Age (month)	Base case: 6 hospitalizations per 1,000 child-years (range: 3–13 hospitalizations)		Ref.
0–5	0.18	(0.0003–0.0044)	8, 12
6–11	0.67	(0.0011–0.0169)	
12–23	1.20	(0.0020–0.0304)	
24–35	0.48	(0.0008–0.0124)	
36–47	0.27	(0.0004–0.0071)	
48–59	0.23	(0.0004–0.0061)	

Table 2. Input parameters

Parameter	Base case (range)		Ref.
Incidence of hospitalizations per 1,000 child-years	6	(3–13)	8, 12
Incidence of outpatient visits per 1,000 child-years	123	(116–126)	7
Duration of illness/absence from work of caregivers			
Hospitalization	5		8, 16
Outpatient visit	2		
Direct medical cost, ¥			
Hospitalization	138,298	(103,724–172,873)	8, 16
Outpatient visit	13,830	(10,373–17,288)	
Productivity loss of caregivers (indirect cost), ¥			
Hospitalization	38,544	(28,908–48,180)	17
Outpatient visit	15,418	(11,564–19,273)	
Utility <12 month of age			
Hospitalization	0.425	(0.330–0.520)	18
Outpatient visit	0.781	(0.678–0.884)	
Utility <24 month of age			
Hospitalization	0.313	(0.190–0.436)	18
Outpatient visit	0.735	(0.616–0.854)	
Utility ≧24 month of age			
Hospitalization	0.200	(0.049–0.352)	18
Outpatient visit	0.688	(0.553–0.824)	
Vaccine efficacy, %			
Hospitalization	95	(83.8–99.5)	19, 20
Outpatient visit	85	(76.8–88.9)	
Vaccine cost per course, ¥	20,000	(15,000–25,000)	21
Annual discount rate, %	5	3	22

assumed to be ¥38,544 and ¥15,418 for rotavirus-associated hospitalization and outpatient visit, respectively, by applying the same figures reported in a cost-effectiveness study for the varicella vaccine in Japan (17).

Impact on the quality of life: We applied the estimate of the utility of care in the UK for different health states associated with rotavirus gastroenteritis (18) to our model birth cohort with an adjustment for the age group (Table 2): a median of the utility of care for children younger than 18 months and that for children aged between 18 months and 5 years in the UK study (18) was applied for children aged between 12 months and 23 months in this study.

Vaccine efficacy and cost: We assumed that the complete course of Rotarix (2 doses) or RotaTeq (3 doses) would be given to all children when they were 0–5 months of age and that the rotavirus vaccine was administered concomitantly with other vaccines in the routine childhood immunization schedule. The same efficacy levels were assumed for both vaccines: 95% and 85% efficacy against rotavirus-associated hospitalizations and outpatient visits, respectively, after the full doses were administered (19,20). Further, the same vaccination cost of ¥20,000 per course was assumed for both vaccines, in accordance with the CDC price list (21) and including the cost of administration. Under the assumption of the concomitant administration of rotavirus vaccine with other childhood vaccines, the productivity loss of the caregivers due to hospital visits for rotavirus vaccination was not considered separately.

Discount rate: The costs and the quality of life of rotavirus-associated hospitalizations and outpatient visits were discounted at an annual rate of 5% (22).

Cost-effectiveness evaluation: The rotavirus immunization program was considered cost-effective if the ICER was less than ¥6 million per QALY gained (23).

Sensitivity analysis: We sought to determine whether the outcome regarding the cost-effectiveness would change by applying a range of incidences of rotavirus-associated hospitalizations, from 3 to 13 hospitalizations per 1,000 child-years (Table 2). We assumed that the variation in the incidence of the hospitalizations was primarily due to the local difference in healthcare utilization practices rather than at difference in the incidence of severe rotavirus gastroenteritis. Thus, the total number of children seeking medical care due to rotavirus gastroenteritis was set a constant value of 129 cases per 1,000 child-years: 6 hospitalizations and 123 outpatient visits for the base case scenario. Thus, when the incidence of rotavirus-associated outpatient visits was changed to 116, for example, the incidence of hospitalizations was adjusted to 13 hospitalizations per 1,000 child-years. The influences of the changes in other parameters were examined in a one-way sensitivity analysis by using the range shown in Table 2: the direct medical cost and the productivity loss per case (±25% from the base case), the utility (95% confidence interval [CI] [18]), the vaccine efficacy (95%CI [20]), the vaccine cost per course (±25% from the base case), and the discount rate (3% used in studies conducted in other industrialized countries [24–26]).

RESULTS

Base case: In the absence of a universal rotavirus immunization program, the number of rotavirus-associated hospitalizations and outpatient visits were estimated to be 32,900 and 678,218, respectively, when the model birth cohort of 1.1 million children was followed for 5 years (Table 3). The direct medical cost was ¥13 billion from the healthcare perspective, whereas the indirect cost was ¥11 billion. Thus, the economic burden of rotavirus gastroenteritis was calculated to be ¥24 billion from the perspective of the society. When those costs were broken down, 67% of the direct medical cost was associated with outpatient visits from the healthcare

Table 3. Base case results

Outcome	No program	With program	Difference	Reduction, %
No. of events				
Hospitalizations	32,900	1,592	−31,308	95
Outpatient visits	678,218	101,731	−576,487	85
Direct medical cost, ¥				
Hospitalizations	4,281,782,278	207,097,440	−4,074,684,838	95
Outpatient visits	8,828,124,134	1,324,196,483	−7,503,927,651	85
Indirect medical cost, ¥				
Hospitalizations	1,193,343,477	57,718,577	−1,135,624,900	95
Outpatient visits	9,841,794,497	1,476,244,496	−8,365,550,001	85
Vaccination cost, ¥	0	22,000,000,000	22,000,000,000	
Total cost, ¥				
Healthcare system	13,109,906,412	23,531,293,923	10,421,387,511	−79
Societal	24,145,044,386	25,065,256,995	920,212,609	−4
QALY loss	1,219	153	−1,066	87
ICER per QALY gained, ¥				
Healthcare system	9,780,524	(Not cost-effective)		
Societal	863,624	(Highly cost-effective)		
Break even price per course, ¥				
Healthcare system	10,526			
Societal	19,163			

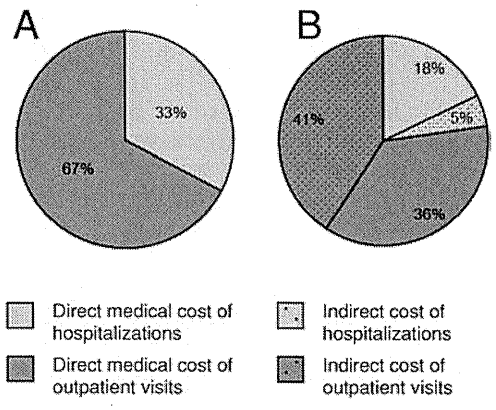

Fig. 1. Cost structure of rotavirus hospitalizations and outpatient visits before the implementation of rotavirus vaccination program. (A) the healthcare perspective and (B) the societal perspective.

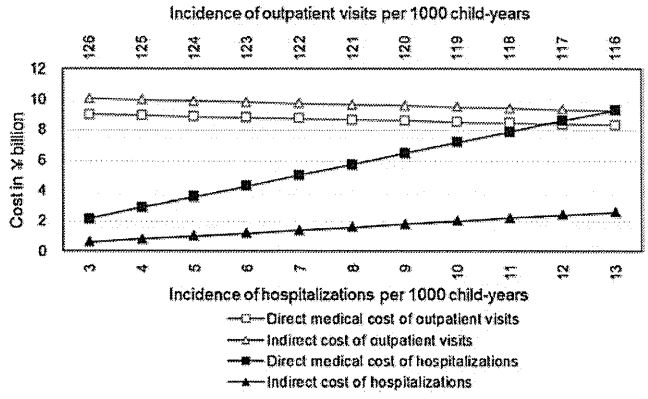

Fig. 2. The direct medical cost and the indirect cost of rotavirus hospitalizations and outpatient visits according to the incidence of the hospitalizations and outpatient visits.

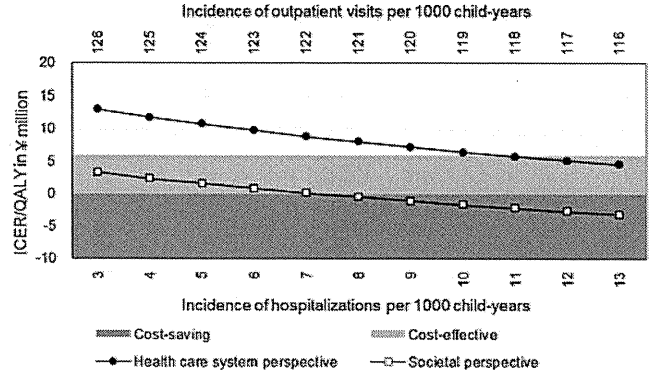

Fig. 3. Sensitivity analysis result. The ICER per QALY gained from the perspective of healthcare system and society according to the incidence of rotavirus hospitalizations and outpatient visits. The area shaded with light gray and dark gray shows the cost-effective (less than ¥6 million per QALY gained) and cost-saving (less than ¥0), respectively.

perspective (Fig. 1A), while 77% (36% for the direct medical cost and 41% for the indirect cost) of the societal cost was attributable to outpatient visits from the societal perspective (Fig. 1B).

Considering the inclusion of rotavirus vaccination in the routine immunization program, we found that the number of rotavirus-associated hospitalizations and outpatient visits decreased by 85% to 1,592 and to 101,731, respectively (Table 3). However, the direct medical cost increased to ¥24 billion because ¥22 billion was the immunization cost. The indirect cost decreased to ¥2 billion. The universal immunization program reduced the QALY loss from 1,219 before the introduction of the vaccine to 153 after the universal immunization. Thus, the ICER per QALY gained was calculated to be ¥9.8 million from the healthcare perspective and ¥900,000 from the societal perspective, which indicated that rotavirus vaccination was highly cost-effective (Table 3). The break-even price of rotavirus vaccine was ¥10,526 and ¥19,163 per course from the healthcare perspective and the societal perspective, respectively.

Sensitivity analysis: The changes in healthcare utilization practices from hospital admission to outpatient care had the greatest impact on the direct medical cost of rotavirus-associated hospitalizations: a minimum of ¥2 billion at 3 hospitalizations per 1,000 child-years and a maximum of ¥10 billion at 13 hospitalizations per 1,000 child-years (Fig. 2). From the healthcare perspective, the universal rotavirus immunization program was cost-effective when the incidence of rotavirus-associated hospitalizations was 11 or larger per 1,000 child-years (Fig. 3). From the societal perspective, it was cost-effective when the incidence of the hospitalizations was 3 or larger per 1,000 child-years. The universal rotavirus immunization program was even rendered cost-saving when the incidence of rotavirus-associated hospitalizations was 8 or larger per 1,000 child-years.

The most influential parameters that affected the results of cost-effectiveness analysis were the vaccine cost per course and the combined incidence of rotavirus-associated hospitalizations and outpatient visits (Fig. 4). From the perspective of the healthcare system, the universal rotavirus immunization program was cost-effective, with an ICER of ¥4.6 million per QALY gained when the vaccine cost was reduced to ¥15,000 per course (Fig. 4A). From the societal perspective, the universal immunization program was cost-effective and cost-saving for any value of the input parameters, except when the vaccine cost was its upper limit of ¥25,000 per course. Even in this extreme scenario, the ICER per QALY gained was calculated to be ¥6.03 million, a value almost identical with the cost-effectiveness threshold of the immunization program, which is ¥6.0 million (Fig. 4B).

DISCUSSION

The economic burden of rotavirus-associated hospitalizations and outpatient visits among children aged less than 5 years in Japan was calculated to be ¥13 billion and ¥24 billion per year from the perspective of the healthcare system and the society, respectively, (Table 3). Rotavirus-associated outpatient visits accounted for a much larger part of the economic burden than rotavirus-associated hospitalizations: 67% of the direct medical cost and 77% of the societal cost (Fig. 1). However, the incidence of rotavirus-associated hospitalization was more sensitive to the results of the cost-effectiveness analysis than the incidence of outpatient visits (Figs. 2 and 3). The universal rotavirus im-

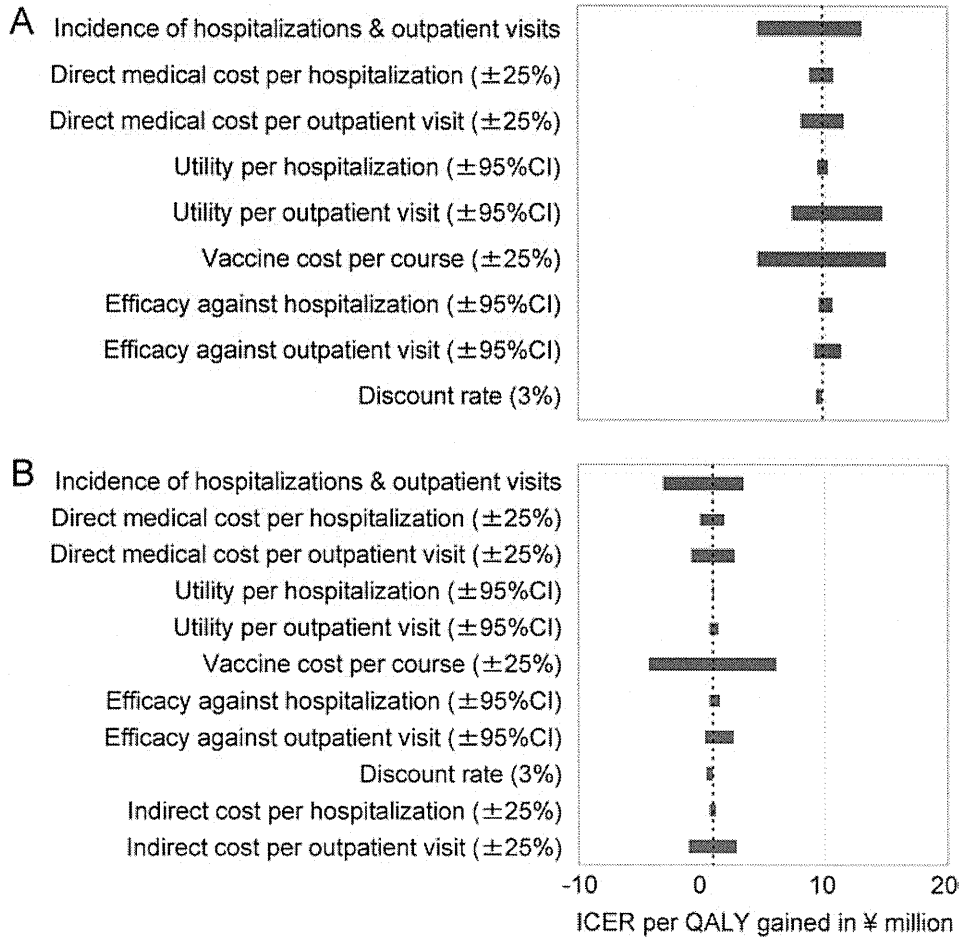

Fig. 4. Sensitivity analysis result. The ICER per QALY gained according to input parameters. (A) the healthcare perspective and (B) the societal perspective. The dotted line shows an ICER of (A) ¥9,780,524 and (B) ¥863,624 per QALY gained for the base case.

munization program was found to prevent 85% of the hospitalizations and outpatient visits due to rotavirus gastroenteritis. For the base case, the ICER was ¥9.8 million per QALY gained from the healthcare perspective, and the immunization program was highly cost-effective, with an ICER of ¥900,000 per QALY gained from the societal perspective. The immunization program was likely to be cost-saving from the societal perspective if the vaccine cost was reduced to ¥19,163 per course. This vaccine cost appeared to be achievable because this break-even price was only ¥837 less than the price used for the base-case scenario set in consultation with the CDC list price (21). The rotavirus immunization program was cost-effective and cost-saving from the societal perspective, for all the values of incidence of rotavirus-associated hospitalizations reported previously in Japan (Fig. 3). The vaccine cost and the combined incidence of rotavirus-associated hospitalizations and outpatient visits were the most influential parameters affecting the results of the cost-effectiveness analysis, which ranged from cost-saving to cost-effective with the threshold value of ¥6.0 million for an ICER per QALY gained from the societal perspective (Fig. 4). It is, therefore, recommended that the rotavirus vaccine should be incorporated into the childhood immunization schedule in Japan as soon as after the licensure of either of the rotavirus vaccines.

The estimated incidences of rotavirus-associated hospitalizations ranged from 3.8 to 13.2 per 1,000 child-years in Japan (8,12). This variation in the incidence was similar to that in the incidences of rotavirus-associated hospitalizations in the cost-effectiveness analyses conducted in other industrialized countries: from 2.5 hospitalizations per 1,000 child-years in Netherlands (27) to 14.6 hospitalizations per 1000 child-years in Taiwan (26). Although the incidence of hospitalization has been recognized as an influencing parameter in industrialized countries (11), few studies have applied different estimates of the incidence of rotavirus-associated hospitalizations in the sensitivity analysis of the cost-effectiveness analyses of rotavirus vaccine (26,28). In Australia, for example, where rotavirus vaccine was introduced into the universal immunization program since 2007, a cost-effectiveness analysis showed that the ICER per QALY gained from the implementation of the immunization program was lesser than the maximum cost-effectiveness threshold when the base case incidence of rotavirus-associated hospitalizations was applied (28).

The economic burden of outpatient visits due to rotavirus gastroenteritis in Japan was twice and 8 times larger than that of the rotavirus-associated hospitalizations from the healthcare perspective and the societal perspective, respectively (Table 1). The base case inci-

dence of 123 outpatient visits per 1,000 child-years and the direct medical cost of US$109 per outpatient visit in Japan (The value of ¥13,830 per outpatient visit was inflated to the value for the year 2006 and converted to US$ by using the purchasing power parity [29]) was larger than that in 10 other industrialized countries (18,24-28,30-34): a median of 28 outpatient visits per 1,000 child-years (interquartile range [IQR] 23-46, including hospital outpatient visits and other primary cares due to rotavirus gastroenteritis) and a median of US$46 (IQR US$33-81) per visit. The proportion of the cost of outpatient visits in Japan (Fig. 1) was also greater than that in other industrialized countries (18,25,26,30,31,33): the proportion of the cost of the hospitalizations was the greatest in the total cost from the healthcare perspective (62% for the hospitalizations, 20% for the emergency department visits, and 18% for the outpatient visits) as well as the societal perspective (44%, 21%, and 35%, respectively). It is expected that the implementation of the rotavirus immunization program in Japan will substantially reduce the cost of outpatient visits. In this regard, monitoring of not only hospitalizations but also outpatient department visits due to rotavirus gastroenteritis will be important in epidemiological surveillance in Japan.

We assumed that Rotarix (2 doses between 6 and 24 weeks of age [35]) or RotaTeq (3 doses between 6 weeks and 8 months of age [35]), was administered concomitantly with other vaccines to children in the first 6 months of life in this model birth cohort. However, the co-administration is not viable without modifications of the routine childhood immunization schedule in Japan because the earliest immunization is commonly the BCG vaccine administered at the 3rd month. Thus, we evaluated the cost-effectiveness of the immunization program for the condition where caregivers were absent from their work for a separate visit to the hospital for rotavirus vaccination. The productivity loss arising from the rotavirus immunization was estimated at ¥7,709 and ¥11,563 per course of Rotarix and RotaTeq, respectively, under the assumption that caregivers took a half day off from work per dose, and the wage was calculated based on an economic study of varicella immunization (17). For the base case considering the productivity loss for the rotavirus immunization, the immunization program was not cost-effective, with an ICER of ¥8.8 million and ¥12.8 million per QALY gained for the Rotarix and RotaTeq immunization programs, respectively, from the societal perspective. Therefore, the choice of Rotarix since it requires fewer doses will substantially reduce the productivity loss due to the immunization. A concurrent immunization schedule of rotavirus vaccine with other existing vaccines needs to be arranged to retain the cost-effectiveness of the universal rotavirus immunization program in Japan.

There are several limitations to this study. First, we did not consider any effects that may arise from the differences in the serotypes. However, even if the serotype specificity in rotavirus infection and the vaccine efficacy against each serotype is taken into account, the result may not be much different because the serotype-specific efficacies were similar for most of the serotypes circulating in Japan (36,37). Second, the events of rotavirus deaths, nosocomial infections, and home care cases were not included because of the non-availability of the relevant data. Third, this model did not take herd immunity into account. Indirect effect of rotavirus vaccine may have caused larger reduction in rotavirus disease burden than expected after the implementation of the universal rotavirus immunization program (5,6,38,39). If the model used in this study could include the effect of herd immunity, the cost-effectiveness result would become more favorable to the implementation of the rotavirus immunization program.

In conclusion, by applying the Markov model, the economic burden of rotavirus-associated hospitalizations and outpatient visits among children aged less than 5 years before the introduction of rotavirus vaccination in Japan was estimated to be ¥13 billion and ¥24 billion from the healthcare perspective and the societal perspective, respectively. A universal rotavirus immunization program would prevent 85% of the rotavirus-associated hospitalizations and outpatient visits. For the base case scenario, the universal rotavirus immunization program was found to almost cost-effective from the healthcare perspective, with the vaccine cost assumed to be ¥20,000 per course, and it was highly cost-effective with an ICER of ¥900,000 per QALY gained from the societal perspective. The universal rotavirus immunization program was found to be cost-effective from the societal perspective even at the lowest value reported for the incidence of rotavirus-associated hospitalizations: an ICER of ¥3.3 million per QALY was gained when the incidence of rotavirus-associated hospitalization was 3 per 1,000 child-years. It was also found to be cost-saving when the incidence of rotavirus-associated hospitalization was 8 or larger per 1,000 child-years. A caveat in this cost-effective analysis is that all scenarios considered to be under the assumption of co-administration of the rotavirus vaccine with other childhood vaccines, which is common practice worldwide. Therefore, the arrangement of the routine childhood immunization program such that the rotavirus vaccine is administered concomitantly with other childhood vaccines is imperative.

Conflict of interest None to declare.

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REVIEW

Rotarix in Japan: Expectations and Concerns

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ABSTRACT

A live-attenuated, orally-administered, monovalent, human rotavirus vaccine, Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), was licensed and launched in 2011 as the first rotavirus vaccine in Japan. The rotavirus causes a substantial disease burden with an estimated 790,000 outpatient visits, 27,000-78,000 hospitalizations, and approximately 10 deaths each year in Japan. Since a recent clinical trial showed that Rotarix was as efficacious in Japan as in other industrialized countries, it is expected that the annual number of rotavirus hospitalizations will be reduced to between 1000-3000, and that outpatient visits will be reduced to 200,000. The universal rotavirus immunization program with Rotarix was calculated to be at the threshold of being cost-effective, even from the healthcare perspective, and it was highly cost-effective from the societal perspective, assuming that Rotarix is co-administered with other childhood vaccines. While Rotarix contains only a single G1P[8] human rotavirus, the postlicensure studies in Brazil showed that Rotarix provided a 75%-85% protective efficacy against severe dehydrating diarrhea or hospitalizations due to fully-heterotypic G2P[4] strains. While postlicensure studies detected a small and finite risk of intussusception associated with the administration of Rotarix, the authors conclude that Rotarix is safe to administer to infants between 6-12 weeks of age for the first dose and by 24 weeks of age for the second dose. However, the authors strongly discourage the delayed administration of the first dose between 13-20 weeks of age, which is allowed without any warning. Given the high incidence of naturally-occurring intussusception in Japan (185 cases per 100,000 children/year among children less than 1 year of age), this should prevent pediatricians and parents from having ill-perceptions of Rotarix being associated with an increased number of temporally-associated

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intussusception, and fully appreciate the benefit of the rotavirus vaccine.

Keywords: diarrhea; heterotypic immunity; immunization; intussusception; Japan; Rotarix; rotavirus

INTRODUCTION

Acute diarrhea is the leading cause of childhood morbidity and mortality worldwide, accounting for approximately 15% of deaths occurring in children less than 5 years of age.[1] Rotavirus has been recognized as the single most important etiological agent of severe diarrhea[2] causing an estimated 453,000 deaths annually.[3] Thus, after reviewing the recent efficacy data generated by studies on Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) in African countries, the Strategic Advisory Group of Experts of the World Health Organization (WHO) in 2009 recommended incorporation of rotavirus vaccines into the national immunization programs of all countries, with an emphasis in those regions where mortality rates in children less than 5 years of age are ≥10%.[4-6] Two major rotavirus vaccines that were prequalified by the WHO are the monovalent, human rotavirus-based vaccine, Rotarix,[7] and the pentavalent, bovine-human re-assortant vaccine, RotaTeq® (Merck & Co, Inc., NJ, USA).[8] These rotavirus vaccines are licensed in more than 120 countries, but it was not until 2011 that the Ministry of Health, Labor, and Welfare in Japan approved the rotavirus vaccine (Rotarix) for use in infants to prevent rotavirus gastroenteritis. In this review the authors briefly describe two important issues to understand the rotavirus vaccine: the nature of protective immunity after natural rotavirus infection and the burden of rotavirus diarrhea in Japan. The authors then concisely summarize the product profile of Rotarix that is most relevant in practice. Finally, the authors address two key issues for practitioners and parents: the efficacy of Rotarix against fully heterotypic strains and the safety of Rotarix with respect to intussusception.

ROTAVIRUS AND ITS SEROTYPES

Rotavirus, taxonomically a species *(Rotavirus A)* within genus *Rotavirus*, family *Reoviridae*, is a nonenveloped RNA virus with icosahedral symmetry.[9] The outer surface of the virion consists of viral spikes (made up of the VP4 trimers) and the outercapsid proteins (made up of the VP7 trimers).[9] Both VP4 and VP7 independently serve as a neutralization antigen, and define the protease-sensitive protein (P) type and the glycoprotein (G) type, respectively.[2,9] While serotype should, by definition, be determined by serologic assays, molecular assays have replaced serologic assays in the determination of G and P types of a rotavirus in clinical specimens; hence, referred to as the genotype.[9] While there is an exact match between G serotype and G genotype, different numbering systems were adopted to designate P serotype and P genotype, with P genotype being designated within squared brackets. Thus, the P serotype of RIX4414, the vaccine strain in Rotarix, is P1A, whereas its P genotype is P[8]. There are 27 G genotypes and 35 P genotypes described to date,[10] but the G and P type combinations detected in human rotaviruses are mostly limited to G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8].[11,12] However, previously rare G12 strains appear to have emerged across the globe[13-15] and G8 strains, with either P[6] or P[4], account for a significant proportion of human rotavirus strains in Africa.[16,17] Such genetic diversity appears to be generated by frequent reassortment of the genome segments and interspecies transmission of rotaviruses between humans and animals.[18-21]

PROTECTIVE IMMUNITY AFTER NATURAL INFECTION AND THE GUIDING PRINCIPLE OF ROTAVIRUS VACCINES

Complete protection against moderate-to-severe rotavirus-associated diarrhea, but not against mild diarrhea or infection itself, is obtained after asymptomatic infection in the neonatal period[22] or after two infections with rotavirus, regardless of whether the infections are symptomatic or asymptomatic.[23] In a cohort study in Mexico,[23] the adjusted efficacy in protecting against subsequent rotavirus infection was 38% after one infection, 60% after two infections, and 66% after three infections. In contrast, the efficacy against rotavirus-associated diarrhea of any severity was 77% after one infection, 83% after two infections, and 92% after three infections. Against moderate-to-severe rotavirus-associated diarrhea, protection is greater with 87% after one infection and 100% after two or three infections. In the same study, repeated infections with the same G type were less likely to occur, suggesting the presence of homotypic immunity. It is generally believed that, while infection with one serotype provides serotype-specific (homotypic) protection, repeated infections tend to provide broader protection that exerts over different serotypes; ie, heterotypic protection.[24] Thus, it is clear from the natural history of rotavirus infection that the aim of the rotavirus vaccine should be to prevent severe, dehydrating diarrhea and deaths due to rotavirus infection in the first 3 years of life when rotavirus-associated diarrhea is most severe, rather than to prevent mild diarrhea or infection.[25] However, this guiding principle was challenged by a recent study in India that showed a much lower protection effect of natural rotavirus infection against subsequent diseases in a setting with high viral load and diversity.[26]

THE BURDEN OF ROTAVIRUS DIARRHEA IN JAPAN

Given that the aim of the rotavirus vaccine is to reduce the burden of rotavirus-associated diarrhea in the society, the key information is the annual number of cases of rotavirus-associated diarrhea and the associated cost. The cost needs to be viewed from both the healthcare and the societal perspectives. With regard to the annual number of cases of rotavirus-associated diarrhea, the most important is the number of rotavirus hospitalization at a national level and whether the estimated reduction of the disease burden will be cost-effective. The major difference between the cost calculated from the healthcare perspective and that calculated from the societal perspective is that the latter includes the productivity loss of care-givers of sick children. This productivity loss accounts for the vast majority of the indirect cost associated with rotavirus-associated diarrhea.[27,28]

The birth cohort in Japan is approximately 1 million and the information required is the number of children who will be hospitalized due to rotavirus-associated diarrhea when the cohort is followed for 5 years. Only a few studies are available in Japan, and it was estimated that there were 790,000 outpatient visits,[29] 27,000-78,000 hospitalizations,[30-32] and approximately 10 deaths due to rotavirus gastroenteritis in the entire country. The variability in the estimate of the annual number of rotavirus hospitalizations was due to the variability in the incidence of rotavirus hospitalizations in different locations and dates in Japan: 4.9 per 1000 children/year in the Mie prefecture between 2003-2007,[30] 5.3 per 1000 children/year in the Kyoto prefecture between 2008-2010,[31] and 13 per 1000 children/year in the Akita prefecture between 2001-2002.[32] These variable incidences, however, were not dissimilar from those reported from other industrialized

countries; for example, in seven European countries that included Belgium, France, Germany, Italy, Spain, Sweden, and the UK (the REVEAL study), the incidence ranged from a minimum of 2.9 per 1000 children/year in the UK to a maximum of 9.9 per 1000 children/year in Belgium, with a median of 6.5 per 1000 children/year in Spain.[33,34]

If the rotavirus vaccine is as efficacious in Japan as in other industrialized countries, it is expected that the annual number of rotavirus hospitalizations could be reduced to between 1000-3000, and that the number of the outpatient visits could be reduced to 200,000. To determine whether this reduction will be cost-effective, one needs to calculate the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained. In Japan, a prevention measure is said to be cost-effective if its ICER per QALY gained is JPY 6 million. From a healthcare perspective, the universal rotavirus immunization program with Rotarix was calculated to be almost at the threshold of being cost-effective, assuming the vaccine cost of JPY 20,000 per course. From the societal perspective, it was highly cost-effective with an ICER of JPY 900,000 per QALY gained.[28] A caveat to this analysis is that the authors assumed co-administration of Rotarix with other childhood vaccines. However, co-administration is unpopular under the current situation in Japan (see later). If given independently from other vaccines, the productivity loss arising from the rotavirus immunization would become substantial, and the rotavirus vaccination would be less cost-effective, with an ICER of JPY 8.8 million per QALY gained.[28]

PRODUCT PROFILE OF ROTARIX

Indications

Rotarix is indicated for the prevention of rotavirus gastroenteritis. Its protective efficacy is suggested against rotavirus strains carrying G1P[8], G2P[4], G3P[8], G4P[8], or G9P[8].[35]

Product Specifications of Rotarix

Rotarix contains a live-attenuated G1P[8] human rotavirus strain, RIX4414, that contains at least 1 million median cell culture infective dose ($CCID_{50}$) in 1.5 mL of calcium carbonate buffer. While a ready-to-use liquid formulation is a welcome addition, a 50% increase in volume from the formulation that requires reconstitution (1 mL) may present technical inconvenience to the oral administration of the liquid into the mouth of small infants of as early as 6 weeks of age. This larger volume of the liquid formulation relates to the content of sucrose (excipient) in the liquid formulation, which is higher than that used in the lyophilized vaccine that is reconstituted with 1 mL of calcium bicarbonate buffer.[36]

The Standard Schedule and the Upper Limits of Age for Administration

Rotarix is to be administered orally in a two-dose schedule. According to the package insert,[35] the first dose should be administered to infants beginning at 6 weeks of age and the second dose should be completed by 24 weeks of age, with an interval of at least 4 weeks between the first and the second dose (Figure 1). The company's official promotion pamphlet clearly illustrates that the period for the first dose is between 6-20 weeks, and that the period for the second dose is between 10-24 weeks.[37]

Globally, the upper-limit of age for the first dose is an important issue that may significantly affect the uptake rate of the vaccine and the increase in the temporally associated cases of intussusception. Naturally-occurring intussusception is rare in the first 3 months of age