Supplemental Digital Content 2. Rationale for Parameter Selection

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The rationale for selecting the numerical values for each item used in this study is described.

Section 1. Incidence

1-1. Incidence (Ambulatory visits + Hospitalization)

In view of Japan's universal health insurance system and pediatric healthcare system, we considered that it is unlikely that patients with rotavirus (RV) infection would be treated at home without consulting a medical institution; thus, this scenario was not considered in this study. Therefore, in the present study, we assumed that a patient suffering from RV would be treated as an ambulatory visit or hospitalized.

Five studies on the incidence of RV gastroenteritis (RVGE) before vaccine introduction were found[1-5]. The outline is as follows.

Author	Year published	Region	Study type	Result	Remarks
Yokoo[1]	2004	Nationwide	meta-analysis	Approximately 790,000 children are affected by six years of age. Age distribution is described.	Adopted in cost-effectiveness analysis studies by Sato[6], Itzler[7], Nakagomi[8], and Hoshi[9].
Onishi[2]	2003	Soma Area, Fukushima Pref.	retrospective	Age distribution is described.	
Nakagomi[3]	2013	Internet survey	retrospective	Age distribution is described.	Adopted in a cost-effectiveness analysis study by Ikeda[10].
Minami[4]	2013	Single clinic in Kagoshima Pref.	retrospective	88.6/1,000 child-years for all ages.	
Kamiya[5]	2014	Mie Pref.	prospective	134.8/1,000 child-years for all ages.	

Three studies[1-3] contain age distributions, which are summarized. The incidence in all ages was 133.3/1,000 child-years, which was in good agreement with the figures of Kamiya[5].

0-year-old	Denominator	N of RV	Probability
Yokoo (<6 mo)	56,741	1,776	0.0313
Yokoo (>6 mo)	56,649	8,571	0.1513
Onishi	2,297	111	0.0483
Nakagomi	26,784	3,107	0.1160
Subtotal	142,472	13,565	0.0952

1-year-old	Denominator	N of RV	Probability
Yokoo	112,782	30,530	0.2707
Onishi	2,329	138	0.0593
Nakagomi	17,649	5,930	0.3360
Subtotal	132,759	36,598	0.2757

2-year-old	Denominator	N of RV	Probability
Yokoo	115,178	12,647	0.1098
Onishi	2,371	48	0.0202
Nakagomi	24,696	6,100	0.2470
Subtotal	142,245	18,795	0.1321

3-year-old	Denominator	N of RV	Probability
Yokoo	115,178	12,647	0.1098
Onishi	2,403	29	0.0121
Subtotal	117,581	12,676	0.1078

4-year-old	Denominator	N of RV	Probability
Yokoo	115,525	5,395	0.0467
Onishi	2,402	14	0.0058
Subtotal	117,927	5,409	0.0459

Assuming that all classes are normally distributed, the upper and lower limits were estimated from the 95% CI.

1-2. RVGE Hospitalization Rate (to the cohort)

Eleven studies reported the RVGE hospitalization rate before the introduction of the vaccines[2,4,11-19]. The outline is as follows.

Author	Year published	Region	Study type	Result	Remarks
Asada[11]	2014	Tsu City, Mie Pref.	prospective	Age distribution is described.	

Nakagomi[12]	2005	Akita Pref.	prospective	7.9-17.6/1,000 child-years for all ages. Age distribution is described.	Adopted in cost-effectiveness analysis studies by Sato[6], Itzler[7], and Nakagomi[8].
Kamiya[13]	2009	Tsu City and Ise City, Mie Pref.	retrospective	3.8-4.9/1,000 child-years for all ages. Age distribution is described, but the actual number is not described.	Adopted in a cost-effectiveness analysis study by Sato[6].
Onishi[2]	2003	Soma Area, Fukushima Pref.	retrospective	Age distribution is described.	
Ito[14]	2011	Kyoto Pref.	retrospective	5.3/1,000 child-years for all ages.	Adopted in a cost-effectiveness analysis study by Nakagomi[8].
Nakagomi[15]	2009	Akita Pref.	retrospective	14.9 (8.2-20.2)/1,000 child-years for all ages.	
Hiramoto[16]	2005	Akita Pref.	prospective	11/1,000 child-years for all ages. Age distribution is described.	For up to 3 years of age.
Kinoshita[17]	2014	Akita Pref.	retrospective	13.7 (6.8-20.7)/1,000 child-years for all ages. Age distribution is described, but the actual number is not described.	
Kamiya[18]	2011	Mie Pref.	prospective	3.1-5.4/1,000 child-years under the age of 2 years.	Adopted in a cost-effectiveness analysis study by Nakagomi[8]. Partial overlap with Asada[11].
Minami[4]	2013	Single clinic in Kagoshima Pref.	retrospective	10.8/1,000 child-years for all ages.	
Yokoo[19]	2009	Internet survey	retrospective	Age distribution is described, but the actual number is not described.	

Previously, it was pointed out that there was a difference in the RV hospitalization rate between Akita Pref. in northern Japan and Mie Pref. in western Japan; however, according to Noguchi et al.[20], this was a regional difference, and not a counting problem.

Since four studies[2,11,12,16] described the age distribution specifying real numbers, they are summarized. Three of them[11,12,16] were prospective studies that examined RV infection at admission. No nosocomial infections were included; thus, the nosocomial infection rate[21] was added according to the ratio described below. The hospitalization rate for all ages was 7.9/1,000 child-years, halfway between northern and western Japan, and was not significantly different from the rest of the literature.

0-year-old	Denominator	N of RV	Probability
Asada	9,473	56.7	0.0060
Nakagomi*	2,129	45.1	0.0212
Onishi	2,297	51	0.0222
Hiramoto (<6 mo)	965	1.2	0.0012
Hiramoto (>6 mo)	926	13.9	0.0150
Subtotal	15,790	167.9	0.0106

1-year-old	Denominator	N of RV	Probability
Asada	9,737	89.1	0.0092
Nakagomi*	2,165	63.7	0.0294
Onishi	2,329	71	0.0305
Hiramoto	1,881	30.1	0.0160
Subtotal	16,112	253.9	0.0158

2-year-old	Denominator	N of RV	Probability
Asada	9,749	54.9	0.0056
Nakagomi*	2,251	24.8	0.0110
Onishi	2,371	22	0.0093
Hiramoto	1,736	16.1	0.0093
Subtotal	16,107	117.8	0.0073

3-year-old	Denominator	N of RV	Probability
Asada	9,744	17.2	0.0017
Nakagomi*	2,153	7.5	0.0035
Onishi	2,403	15	0.0062
Subtotal	14,300	39.8	0.0028

4-year-old	Denominator	N of RV	Probability
Asada	9,940	12.8	0.0013
Nakagomi*	2,134	2.1	0.0010
Onishi	2,402	12	0.0050
Subtotal	14,476	26.9	0.0019

*Study in 2005[12]

Assuming that all classes are normally distributed, the upper and lower limits were estimated from the 95% CI.

1-3. Convulsion Rate (to RVGE Hospitalization)

During RV infection, convulsions may occur without dehydration or electrolyte abnormalities. This was first reported by Moroka[22] in 1982. Unlike normal febrile seizures, they occur even at a normal body temperature and in a cluster. Currently, these are often treated with carbamazepine. No EEG abnormalities are observed, the prognosis is good, and it does not shift to epilepsy. Although convulsions with RVGE are associated with a good prognosis, they are commonly encountered in clinical practice and the associated treatment costs may be different. Thus, in Scenario 2, it was decided to consider this separately from RVGE. Febrile seizure accompanying RVGE was also included.

Four studies[23-26] were found on reports of RVGE-related convulsions. All reports were from a single hospital. The outline is as follows.

Author	Year published	Region	Study type	N of hosp. of all RV causes	Convulsion with RVGE	Remarks
Takashima[23]	2018	Kumamoto Pref.	retrospective	1,202	154 (12.8%)	Researched for 19 years. Including after the introduction of the vaccines.
Takeuchi[24]	2013	Osaka Pref.	prospective?	149	13 (8.7%)	No Sequelae. Immediately after vaccine introduction.
Ono[25]	2014	Shizuoka Pref.	retrospective?	125	19 (15.2%)	
Ogita[26]	2006	Chiba Pref.	retrospective	45	3 (6.7%)	
			Total	1,521	189 (12.4%)	

Assuming that all classes are normally distributed, the upper and lower limits were estimated from the 95% CI.

No description was found for the age distribution, so the values were assumed to be common to all ages.

1-4. Encephalopathy Hospitalization

RV is known to cause encephalopathy, and in Japan, RV is said to be the third most common causative pathogen of encephalopathy in children after influenza virus and human herpes virus type 6[27]. The most common type of RV encephalopathy is “clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)”. Although MERS is reported to be successfully treated in 90% of cases, the burden, sequelae, and deaths due to RV encephalopathy cannot be ignored. These factors were included in Scenario 2.

Eight references[23,28-34] included descriptions of RV encephalopathy. All were retrospective studies. The outline is as follows.

Author	Year published	Region	Research Duration (years)	Response rate (%)	N of reported RV encephalopathy	N of Estimated annual RV encephalopathy*	Remarks
Hoshino[28]	2012	Nationwide	3	51.0	40	26.1	4.0% of all encephalopathies
Kawamura[29]	2014	Nationwide	2	70.5	58	41.1	
Takashima[23]	2018	Single hospital in Kumamoto Pref.	19	-	4	-	1,202 hospitalization for RVGE
Morishima[30]	2009	Nationwide	-	-	40.8	40.8	"RV encephalopathies are 4.0% of 1020 cases per year of all causes." Age distribution is described.
Ito[31]	2015	Kyoto Pref.	5	-	5 (1 other case of cerebellitis)	-	"2.6% of all RV patients had severe central nervous system symptoms."
Goto[32]	2018	Nationwide	2	47	26	22.7	
National Institute of Infectious Diseases[33]	2019	Nationwide	13	-	160	-	Infectious disease outbreak survey
Hattori[34]	2018	Aichi Pref.	5	86.4	24	85.5	Estimated N of annual RV encephalopathy with extrapolating nationwide
					Total of 4 studies[28-30,32]	32.1	

* N of reported RV encephalopathy divided by year and response rate.

After adjusting for the number of years and the response rate based on the four studies[28-30,32] that performed a nationwide survey using a questionnaire method, the total annual

number of RV encephalopathy was estimated to be 32.1.

Based on this total number, we estimated the number of children of each age according to the age distribution reported by Morishima[30]. Assuming that these values are normally distributed, the upper and lower limits were estimated from the 95% CI.

Age	N of reported	Proportion	N of estimated
0	1	3.8%	1.23
1	8	30.8%	9.88
2	6	23.1%	7.41
3	2	7.7%	2.47
4	3	11.5%	3.70
> 5	6	23.1%	7.49
Total	26	100.0%	32.10

1-5. Encephalopathy Death Rate (to Encephalopathy Hospitalization)

Regarding deaths as a prognosis of RV encephalopathy, four studies[28-30,32] were found. All were retrospective nationwide surveys. The outline is as follows.

Author	Year published	N of RV encephalopathies	N of deaths	Probability	Remarks
Hoshino[28]	2012	40	3	0.0750	
Kawamura[29]	2014	58	7	0.1207	
Morishima[30]	2009	40.8	4.08	0.1000	“The fatality rate is less than 10%.”
Goto[32]	2018	26	1	0.0385	
	Total	164.8	15.08	0.0915	

This value was assumed to be normally distributed, and the upper and lower limits were estimated from the 95% CI.

No description was found for the age distribution, so the values were assumed to be common to all ages.

1-6. Encephalopathy Sequelae Rate (to Encephalopathy Hospitalization)

Regarding sequelae of RV encephalopathy, four studies[28-30,32] were found. All were retrospective national surveys. The outline is as follows.

Author	Year published	N of RV encephalopathies	N of sequelae	Probability	Remarks
Hoshino[28]	2012	40	8	0.2000	“5 cases up to moderate, 3 cases severe.”
Kawamura[29]	2014	58	15	0.2586	
Morishima[30]	2009	40.8	15.50	0.3800	“Rate of sequela is 38%.”
Goto[32]	2018	26	10	0.3846	
	Total	164.8	48.50	0.2943	

This value was assumed to be normally distributed, and the upper and lower limits were estimated from the 95% CI.

No description was found for the age distribution, so the values were assumed to be common to all ages.

1-7. Nosocomial Infection Rate (to RVGE Hospitalization)

RV is highly contagious and nosocomial infection often occurs despite standard precautions. Although not included in previous studies, in this study it was included in consideration of the magnitude of the impact.

Five references[21,23,35-37] investigated nosocomial RV infection. All were retrospective studies. The outline is as follows.

Author	Year published	Region	N of RV hosp.	N of Nosocomial infections	Probability	Remarks
Yoshida[35]	2004	Single Hospital in Hyogo Pref.	117	37	0.3162	Decreased due to standard precaution.
Nishimura[36]	2013	Single Hospital in Osaka Pref.	280	12	0.0429	Decreased due to standard precaution.
Takano[37]	2013	Single Hospital in Osaka Pref.	89	9	0.1011	Proceedings

Tajiri[21]	2013	8 hospitals nationwide	643	80	0.1244	Age distribution is described.
Takashima[23]	2018	Single Hospital in Kumamoto Pref.	965	96	0.0995	Data before vaccine introduction.
		Total	2,094	234	0.1117	

Based on this probability, we estimated the probability of each age according to the age distribution reported by Tajiri et al.[21]. In the sensitivity analyses, these values were fixed.

Age	N of RV hosp.	N of nosocomial infections	Crude probability	Adjusted probability
0-1	409	62	0.1516	0.1362
2-3	191	15	0.0785	0.0705
4	43	3	0.0698	0.0627
Total	643	80	0.1244	0.1117

1-8. Death (Without Encephalopathy)

RV infection can cause sudden death through factors other than encephalopathy. It is estimated that 610,000 children died annually worldwide[38]. Although rare in developed countries, it is not zero. In previous studies, only Itzler et al.[7] incorporated this factor.

We estimated it in the following three methods:

1. Estimate based on domestic gastroenteritis death
 - Calculated as 19 by multiplying 46 gastroenteritis deaths[39] by RVGE hospitalization rate[40].
 - Calculated as 17 by multiplying 42 deaths due to intestinal infections under 5 years of age[41] by 40% as the hospitalization rate of RVGE.
2. Estimate based on the number of other developed countries
 - Calculated as 18 by multiplying 1/48,680 as RV infection mortality rate in children under 5 years of age in high-income countries by the population of children under 5 years of age in Japan[17].
 - 10-20 children based on the number of deaths in the United States[43].
3. Estimate based on recent statistics

According to national statistical data[44], the number of gastroenteritis-related deaths in children under 5 years of age is as follows.

Year	Viral			Bacterial	Unknown	Total
	RV	Norovirus	Unknown			
2016	6	4	10	8	16	44
2017	3	4	7	4	19	37
Average	4.5	4	8.5	6	17.5	40.5

When the RV vaccine coverage rate in 2016-2017 is c and the effective rate against death after RV vaccination is p, the RV mortality D_{before} before the start of vaccination and the RV mortality D_{after} in 2016-2017 are:

$$D_{after} = D_{before} * c * (1 - p) + D_{before} * (1 - c), \text{ i.e., } D_{before} = D_{after}/(1 - c * p)$$

Since D_{after} is RV plus (part of "Unknown"), it is considered to be 4.5 (up to 17.5; when half of "Unknown" is RV). Also, assuming that c = 0.6 (0.4 to 0.8) and p = 0.8 (0 to 0.9) based on the RV vaccine coverage rate at this time, D_{before} was calculated to be 8.7 (4.5 to 62.5).

In summary, the number of deaths is expected to be approximately 10. We assigned 10 deaths in the base case, varied between 0 and 20 in the one-way sensitivity analysis, and showed a truncated normal distribution with a standard deviation of 5, and values of 0 or more, in the probabilistic sensitivity analysis.

1-9. Excess Intussusception Incidence (to the cohort)

The previous RV vaccine was withdrawn from the market due to intussusception as a side effect. The current monovalent and pentavalent vaccines are scheduled to be administered by approximately 6 months of age due to concern about the excessive increase in intussusception after this age, when natural intussusception is more likely to occur. Pre-marketing surveillance did not show any increase in intussusception in tens of thousands of patients[45,46]. However, post-marketing studies have occasionally reported a slight increase in intussusception immediately after first administration[47,48]. On the other hand, these papers conclude that there is no increase when patients are observed until one year of age. According to Payne et al., "rotavirus vaccine receipt perhaps triggered 'early-onset' intussusceptions among children biologically predisposed to experience this condition, which would then be followed by a period of compensatory, decreased risk later in infancy"[49]; however, the details are uncertain.

Intussusception is a common disease in children, but its frequency varies from country to country. Among the countries of the world, Japan is considered to have a high incidence

of intussusception[50]. Therefore, there is a possibility that the intussusception caused by the RV vaccine may increase. We therefore decided to incorporate it in Scenario 2. In Japan, death from intussusception is rare[51], and we did not examine intussusception-related death as a result of vaccine side effects.

Six studies[51-56] were found that described the frequency of intussusception in Japan before the introduction of the vaccines. The outline is as follows.

Author	Year published	Region	Study	Denominator	N of Intussusception	Probability	Remarks
National Data[52]	2018	7 Pref., and 2 regions	prospective	18,482	19	0.001028	Before introduction of vaccine. Age-in-month distribution is described.
Miura[53]	2013	Nationwide	retrospective	35,552	51	0.001434	Health insurance claims database
Noguchi[54]	2012	Akita Pref.	retrospective	77,436	122	0.001575	
Takeuchi[51]	2012	Nationwide	retrospective	N/A	N/A	0.00179-0.00191	Administrative database. No real numbers listed.
Nakagomi[55]	2012	Single hospital in Akita Pref.	retrospective	22,150	41	0.001851	
National Institute of Infectious Diseases[56]	2014	8 Pref.	prospective	1,851	1.3	0.000683	A research of Ministry of Health, Labor and Welfare.
			Total of 5 studies[52-56]	155,471	234.3	0.001507	

The following two studies[52,57] described the fluctuation of the incidence rate due to the introduction of the vaccines.

Author	Year published	Region	Study	Results
National Data[52]	2018	7 Pref., and 2 regions	prospective	At 3 months of age, the incidence rate became 34.8 to 63.2/100,000, RR 1.8 (0.9-3.6). Under 1 year of age, the incidence rate became 102.8 to 94.0/100,000, RR 0.9 (0.8-1.0).
Bauchau[57]	2015	Nationwide	retrospective	RR 2.96 within 7 days after first dose of monovalent vaccine. Otherwise (within 30 days) no significant difference.

We used the figures in the national data[52], for which the increase is numerically clear. The average vaccination rate during this period is estimated to be 44.3%[58]. Therefore, it

is estimated that the increase at three months after birth is 8.0/100,000 child-years increase (= (63.2 - 34.8)/12 * (150.7/102.8)/0.443).

However, since the risk ratio for the whole population under 1 year of age is <1 in the National Data[52], and no increase was described in other studies that observed children until 1 year of age[47,48], the lower limit was set to 0 (no increase) in the sensitivity analyses. The upper limit is an increase of 30.6/100,000 child-years (= 34.8 * (3.6 – 1)/12 × (185/102.8)/0.443), where the number of cases of intussusception before the introduction of the vaccine is the Takeuchi value[51] and the RR after the introduction is the maximum value of 3.6 in the National Data[52]. In the probabilistic sensitivity analysis, a truncated normal distribution with a value of 0 or more, average of 8.0, and standard deviation of 11.5, were used.

Section 2. Utility Score

2-1. Utility for Ambulatory visits

The utility score is defined as a value of ≤1 (sometimes a negative value) indicating the state of illness, assuming that the QOL of complete health is 1 and the QOL of death is 0. The integration of this over time corresponds to the quality-adjusted life year (QALY).

According to the "Research guideline for evaluating the cost-effectiveness of vaccination"[59], "Effectiveness index is based on QALY", and cost-effectiveness of RV vaccine was also discussed using QALY in previous studies in Japan[6,7,9]. In this study, we decided to conduct a cost-utility analysis using QALY because of the recommendations in the guidelines and the ease of comparison with previous studies.

However, since it is difficult to calculate utility scores in pediatric diseases, no studies from Japan have included ambulatory visits with RVGE; the following two studies[60,61] were found in our search of the relevant global literature.

Author	Year published	Country	Respondents	Target	Tools and Results (95% CI)	Remarks
Brisson[60]	2010	Canada	196 parents whose children experienced RVGE	children	HUI2*: 0.896 (0.874 - 0.917) VAS**: 0.548 (0.510 - 0.587)	Adopted in a cost-effectiveness analysis study by Itzler[7].
				parents	EQ5D***：0.875 (0.844 - 0.907) VAS**：0.731 (0.690 - 0.772)	
Martin[61]	2008	UK	25 General Physicians	children (<18 mo)	EQ5D***: 0.781 (0.678 - 0.884)	Adopted in cost-effectiveness analysis studies by Sato[6] and Hoshi[9].
				children (>18 mo)	EQ5D***: 0.688 (0.553 - 0.824)	

* HUI2: Health Utility Index Mark2

** VAS: Visual Analogue Scale

*** EQ5D: EuroQOL-5Dimension

Two of the three previous studies in Japan used the UK study; possible reasons included the fact that the UK study was stratified by age, that general physicians who were familiar with pediatric patients performed scoring, and the Canadian study only considered ambulatory visits, and did not consider hospitalization. We therefore used the values from the UK in the present study.

In addition, 1-year-old patients showed averaged numerical values of <18 months and >18 months. This is a calculation similar to the work of Sato et al.[6]. This value was assumed to be normally distributed, and the upper and lower limits were estimated from the 95% CI. In the probabilistic sensitivity analysis, a truncated normal distribution with a value of ≤1 was used.

The Canadian study also calculated the utility value of parents caring for children with RVGE, but in our study the QALY calculation was for children only and did not consider parents.

2-2. Utility for Hospitalization (common to RVGE, Convulsion, and Encephalopathy)

As in the ambulatory visits setting, there have been no studies conducted in Japan on the utility for RVGE hospitalization. Worldwide the results are almost exclusively one of the following. The tool used is EQ5D (EuroQOL-5Dimension).

Author	Year published	Country	Respondents	Target	Results (95% CI)	Remarks
Martin[61]	2008	UK	25 General Physicians	children (<18 mo)	0.425 (0.330 - 0.520)	Adopted in cost-effectiveness analysis studies by Sato[6] and Hoshi[9]. Itzler[7] diverted the utility scores for an ambulatory visit from the previous section.
				children (>18 mo)	0.200 (0.049 - 0.352)	
			25 Pediatricians	children (<18 mo, severe)	0.595 (0.528 - 0.662)	
				children (>18 mo, severe)	0.256 (0.157 - 0.354)	
				children (<18 mo, most severe)	0.634 (0.549 - 0.718)	
				children (>18 mo, most severe)	0.077 (-0.057 - 0.210)	

Considering that two of the three previous studies employed age stratification, general physicians who were familiar with pediatric patients performed scoring, and patients

were divided into ambulatory visits and hospitalized patients, these scores were adopted in this study.

In this study, hospitalized cases were treated as uniform severity if their ages were the same; thus GPs assessments were used instead of stratification of severity by pediatricians. Patients of one year of age showed average numerical values of <18 months and >18 months. These calculations were similar to those of Sato et al.[6]. This value was assumed to be normally distributed, and the upper and lower limits were estimated from the 95% CI. In the probabilistic sensitivity analysis, a truncated normal distribution with a value of ≤1 was used.

Although the Canadian study also calculated the utility of parents caring for RV gastroenteritis, our study only considered QALY for children.

No papers could be found that studied the utility of gastroenteritis convulsions, encephalopathies, and nosocomial infections. Thus, in this analysis, the values of RVGE were substituted.

2-3. Utility for Encephalopathy Sequelae

Two studies[62,63] on encephalopathy sequelae in children were found. The outline is as follows.

Author	Year published	Results
Iwata[62]	2008	They asked 9 experts to estimate the quality of life according to the sequelae of pneumococcal meningitis. The estimated values were 0.310 for paralysis and 0.350 for mental retardation.
Kawamura[63]	2016	The neurological sequelae of RV encephalopathy included paralysis (n=3), mental retardation (n=4), others (n=2), and unknown (n=6).

We could not find any articles on the quality of life in patients with sequelae of RV encephalopathy, so we combined these two reports and calculated the utility score as 0.333, taking into account the types of sequelae. The utility score was determined from the year after the onset. In the sensitivity analyses, a constant value was used.

In addition, Hoshi's cost-effectiveness analysis paper[9] cited a study[64] in which the utility score of sequelae of encephalopathy was 0.570 (95% CI 0.523-0.617). It was not adopted this time because the rationale was not clear.

2-4. Utility for Intussusception

No utility scores could be found for intussusception patients in Japan.

In a cost-utility analysis of the treatment and prognosis of intussusception, Bucher et al. set the utility score of intussusception at 0.73 (95% CI 0.50-0.97)[65]. This was based on the results of the calculation for adult severely ill patients (not necessarily intussusception) by Tsevat et al.[66]

No other results could be found in the range examined, so we used Bucher's values and assumed a normal distribution. The upper and lower limits were estimated from the 95% CI. In the probabilistic sensitivity analysis, a truncated normal distribution with a value of ≤1 was used.

Section 3. Length of Treatment

3-1. Days for RVGE

The following three studies[3,67,68] and two textbooks[69,70] investigated the total course of RVGE (recovery from symptoms) mainly in Japan.

Author/Literature	Year published	Results	Remarks
Nakagomi[3]	2013	More than 60% healed in 4-7 days. However, 25% last 8-14 days.	A retrospective internet survey. The average is estimated to be 6.94 (5.14-8.74) days. Adopted in a cost-effectiveness analysis study by Hoshi[9].
Nishimura[67]	2000	Prescribed for 5.4 days.	Summary of a retrospective study in 2 hospitals in Kyoto Pref.[71]
Kashiwagi[68]	2018	Recovered in 3-9 days.	Review
Nelson TextBook[69]	2020 (21st ed.)	Diarrhea lasts 5-7 days.	
RedBook[70]	2018 (31st ed.)	Symptoms last 3-7 days.	

No data that could be analyzed in a meta-analysis were found. For this reason, in this study, we assumed that the total duration of RVGE was 6 days for base cases, regardless of ambulatory-visit and hospitalized cases (excluding encephalopathy and nosocomial infections), and that there was a uniform distribution of 5-7 days in the sensitivity analyses. This value was used for calculating QALY and indirect medical costs.

3-2. Days of Hospitalization (Including Convulsion)

The following 10 studies[2,12,14,21,24,35,69,72-74] investigated the length of hospital stay for RVGE in Japan.

Author	Year published	Region	Study	n	Results	Remarks

Nakagomi[12]	2005	Akita Pref.	prospective	244	Average 5.2 days.	Adopted in cost-effectiveness analysis studies by Sato[6] and Itzler[7].
Onishi[2]	2002	Soma Area, Fukushima Pref.	retrospective	181	5.4 ± 2.2 days	
Nishimura[69]	1999	2 hospitals in Kyoto Pref.	retrospective	25, 16	2-10 days (average 5.4 days), 3-8 days (average 5.4 days)	2 facilities
Tajiri[21]	2013	8 hospitals nationwide	retrospective	584	Median 5.0 days	Adopted in a cost-effectiveness analysis study by Hoshi[9].
Ito[14]	2011	Kyoto Pref.	retrospective	46	5.4 ± 1.4 days	
Yoshida[35]	2004	Single hospital in Hyogo Pref.	retrospective	80	Approx. 6 days	
Takeuchi[24]	2013	Osaka Pref.	prospective?	149	7.5 ± 2.1 days	3.0 ± 1.5 days until hospitalization.
Kimura[72]	2019	Administration DB/Insurance DB	retrospective	N/A	Median 4-5 days	
Kurosawa[73]	2020	Single hospital in Kanagawa Pref.	retrospective	16	5.69 ± 1. 66 days	
National statistics[74]	2017		retrospective		6.1 days for viral GE, 8.1 days for epilepsy, 3.9 days for febrile convulsions.	

Due to the difficulty of performing a meta-analysis, this study estimated the length of hospital stay to be five days. In the sensitivity analyses, it was treated as a constant value.

3-3. Additional Days of Hospitalization for Nosocomial Infection

Outbreaks of nosocomial RVGE infection often require treatment for RVGE in addition to the usual length of hospital stay. Nosocomial infections have a different duration of

treatment from out-of-hospital infections, and are treated separately in Scenario 2.

A single study[21] was reported in Japan regarding additional hospital stay due to RVGE nosocomial infection. In addition, reports from other countries are scattered; however, a summary[75] is presented.

Author	Year published	Results	Remarks
Tajiri[21]	2013	Median 3.0 days (n = 81)	A retrospective study of 8 hospitals nationwide.
Bruijning-Verhagen[75]	2012	2-5 days	A summary of North America and Western Europe.

Due to the difficulty of performing a meta-analysis, the study estimated the length of hospital stay to be three days. In the sensitivity analyses, it was treated as a constant value.

3-4. Days of Hospitalization for Encephalopathy

MERS is common in encephalopathy due to RV infection. No studies on the typical length of stay for MERS could be found. With reference to the expert opinion, we considered the uniform distribution for 10 days in the base case and 7-14 days in the sensitivity analyses.

In a previous study[9], the value of 22.7 days was used, which was based on the length of hospital stay for pneumococcal meningitis[62]; this was not used in the present study.

3-5. Days of Hospitalization for Intussusception

In Japan, the national statistics from 2017[74] indicate that the length of hospitalization in non-invasive cases was 3.2 days (68.8%) and that in invasive cases was 9.6 days (2.5%). In this study, we assumed a non-invasive condition and estimated the length of hospital stay to be three days. In the sensitivity analyses, it was treated as a constant value.

Section 4. Vaccine

4-1. Vaccine Coverage

If the RV vaccine is publicly funded, patients will most likely be co-vaccinated with Hib, pneumococcal, DPT-IPV, and hepatitis B vaccines. RV vaccination will be completed by approximately six months of age. At this age, the patient will have received the third dose of Hib, the third dose of pneumococcus (PCV), and the second dose of DPT-IPV.

Therefore, the coverage rate after the universal RV vaccination was estimated to be close to these coverage rates.

The following two references[76,77] investigated the coverage of these vaccines.

Author	Year published	Region	Universal vaccine name (times)	Coverage rate	Remarks
Sakiyama[76]	2019	Nationwide	Hib (3rd)	94.44% (6 months old) 96.88% (8 months old)	personal communication
			PCV (3rd)	93.86% (6 months old) 96.59% (8 months old)	
			DPT-IPV (2nd)	95.59% (6 months old) 97.66% (8 months old)	
Onogi[77]	2020	Kawasaki City, Kanagawa Pref.	Hib (3rd)	98% (on entering a nursery school*) 98% (all cities**)	* Questionnaire survey. Consider the standard age of vaccination. ** Can exceed 100% due to transfer in and out.
			PCV(3rd)	98% (on entering a nursery school*) 98% (all cities**)	

In the study by Onogi et al.[77], the coverage rate at the time of admission to a nursery school varied according to age, so the value reported by Sakiyama et al.[76] was mainly used in our study.

Based on the above, the cumulative coverage rate when the RV vaccine was publicly funded was estimated to be 94% in the base cases, the upper limit was 98%, and the lower limit was 90% in the one-way sensitivity analysis, and showed truncated normal distribution with a standard deviation of 2% and values of ≤100% in the probabilistic sensitivity analysis. The pattern of incomplete RV vaccination was not considered, and the rest were assumed to be unvaccinated.

4-2. Posteroanterior Ratio for Ambulatory visits

The posteroanterior ratio is the ratio of the change from after introduction of the vaccines to before the introduction of the vaccines (N of after / N of before) among patients with RV infection. This value is calculated as “100% – reduction rate”. If only the direct effect of the vaccine is considered, the reduction rate is calculated as “Vaccine Efficacy * Vaccine Coverage”. Previous studies[6,7,9] have all calculated vaccine efficacy using this method. Scenario 1 deals only with direct effects in this way.

However, the RV vaccines show a much greater reduction than the direct effect due to the herd immunity effect. Although it is difficult to treat herd immunity quantitatively, Kurosawa et al. reported a function that estimates the sum of the direct effects and herd immunity using vaccine coverage as a variable based on multiple clinical data in Japan[78]. Scenario 2 dealt with the sum of the herd immunity effect and the direct effect in this way. In the sensitivity analyses, the values of Scenario 1 and Scenario 2 were set as the upper and lower limits, respectively.

4-3. Posteroanterior Ratio for Hospitalization and Death

For hospitalization and death, the effectiveness for severe RV infection was used. According to the method of calculation used in the previous section, only the direct effect was considered in Scenario 1, and the herd immunity effect was additionally considered in Scenario 2.

Hospitalization is divided into RVGE, convulsion, encephalopathy, and nosocomial infection. Because the effectiveness for convulsion, encephalopathy, nosocomial infection and death are unknown, the values for severe RV infection were also used as for RVGE.

However, according to a nationwide survey, RV encephalopathy may not have decreased[27,79], and sensitivity analyses also considered cases where encephalopathy was not reduced. In other words, it was assumed that the upper limit of the posteroanterior ratio of encephalopathy was 100% in the one-way sensitivity analysis, and that the upper limit was 100% in the probabilistic sensitivity analysis.

Section 5. Cost

5-1. Cost for Ambulatory visit

The following five studies[2,8,69,73,80] were found regarding ambulatory visits direct medical costs of RVGE in Japan.

Author	Year published	Region	Study	n	Results (JPY)	Remarks
Nishimura[69]	1999	2 hospitals in Kyoto Pref.	retrospective	31, 40	15,000, 10,000	2 facilities. Average JPY 12,000. Adopted in cost-effectiveness analysis studies by Sato[6] and Itzler[7].
Onishi[2]	2002	Single hospital in Fukushima Pref.	retrospective	171	19,000	

Nomoto[80]	2014	Single hospital in Hiroshima Pref.	retrospective	12	Approx. 15,000	Read from the graph. Adopted in a cost-effectiveness analysis study by Hoshi[9].
Nakagomi[8]	2013	N/A	N/A	N/A	22,100	Basis of calculation unknown.
Kurosawa[73]	2020	Single hospital in Kanagawa Pref.	retrospective	9	16,000 ± 4,000	
			Total of 4 literature[2,69,73,80]	263	17,000	

Out of these, the ambulatory-visits treatment cost for RVGE was estimated to be JPY 17,000, based on four studies[2,69,73,80] that were clearly based on actual data. In the sensitivity analyses, a triangular distribution with an upper limit of JPY 22,000 and a lower limit of JPY 12,000 was assumed based on the reported values.

5-2. Cost for RVGE Hospitalization

The following six studies[2,12,14,69,72,80] investigated direct medical expenses for hospitalization of RVGE in Japan.

Author	Year published	Region	Study	n	Results (JPY)	Remarks
Nishimura[69]	1999	2 hospitals in Kyoto Pref.	retrospective	25, 16	121,000, 136,000	2 facilities. Average JPY 116,000. Adopted in cost-effectiveness analysis studies by Sato[6] and Itzler[7].
Onishi[2]	2002	Single hospital in Fukushima Pref.	retrospective	181	150,000	
Nomoto[80]	2014	Single hospital in Hiroshima Pref.	retrospective	8	Approx. 147,000	Read from the graph. Adopted in a cost-effectiveness analysis study by Hoshi[9].
Nakagomi[12]	2005	3 hospitals in Akita Pref.	prospective	244	136,000	Adopted in a cost-effectiveness analysis study by Sato[6].
Ito[14]	2011	Single hospital in Kyoto Pref.	retrospective	46	221,000	Adopted in a cost-effectiveness analysis study by Hoshi[9].
Kimura[72]	2019	Administration	retrospective	12,599	Both 200,000-	Assumed average JPY 225,000.

		DB/Insurance DB	/2,137	250,000	
(Ref.) DPC/PDPS*	2019			175,000	Acute gastroenteritis pediatric hospitalization for 5 days with Medical management fee 4/General hospital.
		Total of 6 studies[2,12,14,69,72,80]	15,256	222,000	

* Diagnosis Procedure Combination/Per-Diem Payment System (Japanese version DRG/PPS). A flat-rate payment system per day of hospitalization evaluated based on DPC.

Taken together, we estimate that inpatient treatment costs for RVGE would be JPY 222,000 per course. In the sensitivity analyses, a triangular distribution with an upper limit of JPY 250,000 and a lower limit of JPY 116,000 was assumed based on the reported values.

In addition, the cost estimation from DPC/PDPS was calculated to be JPY 175,000, but the real hospitalization cost would be higher due to various additions such as the function evaluation coefficient, and the approximate values were considered to be the same.

5-3. Cost for Convulsion Hospitalization

No studies could be found on direct medical costs for hospitalization for gastroenteritis convulsion in patients with RV. Calculating the DPC/PDPS medical expenses for "pediatric hospital admission for 5 days with Medical management fee 4/general hospital/no functional evaluation coefficient" for acute gastroenteritis and epilepsy, the results were JPY 175,000 and JPY 212,000, respectively. The latter was 1.21 times the former.

The direct medical cost for hospitalization for RVGE mentioned above was multiplied by 1.21, and the direct medical cost for hospitalization for convulsion with RVGE were estimated to be approximately JPY 269,000 on the base. By the same method, the sensitivity analyses assumed a triangular distribution with an upper limit of JPY 303,000 and a lower limit of JPY 140,000.

5-4. Cost for Encephalopathy Hospitalization

RV encephalopathy is often MERS, and the length of hospital stay is expected to be around 10 days. No literature about direct inpatient medical costs could be found for this. The calculation of DPC/PDPS medical expenses for encephalopathy for "pediatric hospitalization for 10 days with Medical management fee 4/general hospital/no function evaluation coefficient" amounted to approximately JPY 320,000. This was used in the base case and was kept constant in sensitivity analyses.

In a previous study[9], the cost was JPY 852,642, which was based on the hospitalization cost of pneumococcal meningitis[62] and was not used in the present study.

5-5. Cost for Encephalopathy Sequelae

Some RV encephalopathies have sequelae. No studies on direct medical costs of sequelae of RV encephalopathy could be found.

A previous study[9] set the price at JPY 420,464, which is based on the cost of pneumococcal meningitis[62]. The costs of sequelae after pneumococcal meningitis and RV encephalopathy are thought to be similar; thus, our study also used this value.

According to Kawamura et al., the neurological sequelae of RV encephalopathy were paralysis (n=3), mental retardation (n=4), others (n=2), and unknown (n=6)[63]. According to the above-mentioned reference[62], the annual medical expenses for individuals of ≥3 years of age are JPY 292,972 for paralysis and JPY 424,807 for mental retardation. In our study, the direct medical cost for sequelae of encephalopathy was estimated to be about JPY 368,000 per year, and was calculated from the year after the onset. This value was kept constant in the sensitivity analyses.

5-6. Cost for Nosocomial Infection

According to Tajiri et al. [21], additional RV nosocomial hospitalization for 3 days costs JPY 73,150. This is about one-third of the usual RVGE hospitalization cost, but seems reasonable when added to the treatment costs for the underlying disease. This was used in the base case and was kept constant in sensitivity analyses.

5-7. Cost for Intussusception

Regarding the direct medical costs for intussusception, Ikeda et al.[10] reported that the average direct medical cost of 423 hospitalized patients was JPY 299,667. However, this was considered to include surgical cases. In this study, the treatment of intussusception that occurred was assumed to be non-invasive only; thus, the direct medical costs were considered to be lower.

DPC/PDPS medical expenses for intussusception for “pediatric hospitalization for 3 days with medical management fee 4/general hospital/no function evaluation coefficient" were calculated to be approximately JPY 100,000. Based on this value, we assumed a triangular distribution with an upper limit of JPY 200,000 and a lower limit of JPY 50,000

in the sensitivity analyses.

5-8. Indirect Cost

Opinions are divided on how to incorporate indirect costs in calculations from the societal perspective, and each study varies widely. Previous studies on the cost-effectiveness of RV vaccines each deal with:

Author	Year published	Results
Sato[6]	2011	JPY 7,709 (5,782-9,637) per day for labor loss. Hospitalization 5 days, ambulatory visits 2 days.
Itzler[7]	2013	Hospitalization: JPY 8,505 per day * 2.5 days. Ambulatory visits: JPY 3,611 per day * 2.5 days
Nakagomi[8]	2013	JPY 1,911 per hour for labor loss from “regular wages for men and women and regular working hours per month”.
Ikeda[10]	2016	Same as Nakagomi[8].
Hoshi[9]	2016	JPY 1,402 per hour (estimated from the average wage for a woman in 2013)[81]: 56 hours for an ambulatory visit and 10 hours for hospitalization.

The “Research guideline for evaluating the cost-effectiveness of vaccination” in 2017[59] states that “When labor productivity loss is included in the analysis, it is basically based on the estimation using the human capital method that is caused by medical technology.”, and “Time, costs, etc. unrelated to the reduction of work and housework shall not be included.” The latest research by Hoshi[9] is the most near. Hoshi et al. mentioned “Caregiver’s absent working days for outpatient episode was assumed seven days (8 working hours per day), for hospitalized episode5 hospital days (2 hours per day to visit and comfort the patient) plus one absent working day before and after hospitalization, respectively (stated in context).” We performed our calculation according to this figure in this study. In addition, based on the wage census of 2018[81], the basis changed to JPY 1,492 per hour. This value was used as a constant in the sensitivity analyses.

References

1. Yokoo M, Arisawa K, Nakagomi O. Estimation of annual incidence, age-specific incidence rate, and cumulative risk of rotavirus gastroenteritis among children in Japan. *Jpn J Infect Dis*. 2004;57:166–171.

2. Onishi N, Hosoya M, Kawasaki Y, et al. [Epidemiologic study on infectious enteritis, especially rotavirus enteritis in Soma, Fukushima Prefecture, Japan]. *The Journal of Pediatric Infectious Disease and Immunology*. 2002;14:349–353. [in Japanese]
3. Nakagomi T, Kato K, Tsutsumi H, et al. The burden of rotavirus gastroenteritis among Japanese children during its peak months: an internet survey. *Jpn J Infect Dis*. 2013;66:269–275.
4. Minami T. [Rotavirus infection before the introduction of rotavirus vaccines in one year of the pediatric outpatient clinic]. *Japanese Journal of Pediatrics*. 2013;66:123–127. [in Japanese]
5. Kamiya H, Kawano Y, Ito H, et al. [Rotavirus gastroenteritis surveillance –Aiming at introduction and evaluation of evidence-based vaccines– Infectious Agents Surveillance Report]. Available at: https://www.niid.go.jp/niid/ja/iasr-sp/2261-related-articles/related-articles-409/4482-dj4096.html. Accessed March 13, 2020. [in Japanese]
6. Sato T, Nakagomi T, Nakagomi O. Cost-effectiveness analysis of a universal rotavirus immunization program in Japan. *Jpn J Infect Dis*. 2011;64:277–283.
7. Itzler R, O'Brien MA, Yamabe K, et al. Cost-effectiveness of a pentavalent rotavirus vaccine in Japan. *J Med Econ*. 2013;16:1216–1227.
8. Nakagomi T, Nakagomi O, Tsutsumi Y, et al. [Cost-effectiveness of rotavirus vaccination using direct non-medical costs and opportunity costs estimated from the internet survey data]. *Clinical Virology*. 2013;41:239–250. [in Japanese]
9. Hoshi SL, Kondo M, Okubo I. Economic evaluation of routine infant rotavirus immunisation program in Japan. *Hum Vaccin Immunother*. 2017;13:1115–1125.
10. Ikeda T, Shiroiwa T. [Cost effectiveness of rotavirus vaccine. Japanese Health and Welfare Science Research Results Database]. Available at: https://mhlw-grants.niph.go.jp/niph/search/Download.do?nendo=2014&jigyoId=143121&bunkenNo=201420046A_upload&pdf=201420046A0026.pdf. Accessed March 13, 2020. [in Japanese]
11. Asada K, Kamiya H, Suga S, et al. [Active Surveillance for Hospitalizations due to Rotavirus Gastroenteritis among Children (<5 years) in Tsu City, Mie Prefecture, Japan]. *J Jpn Pediatr Soc*. 2013;117:1851–1856. [in Japanese]
12. Nakagomi T, Nakagomi O, Takahashi Y, et al. Incidence and burden of rotavirus gastroenteritis in Japan, as estimated from a prospective sentinel hospital study. *J Infect Dis*. 2005;192 Suppl 1:S106–110.
13. Kamiya H, Nakano T, Inoue M, et al. A retrospective evaluation of hospitalizations for acute gastroenteritis at 2 sentinel hospitals in central Japan to estimate the health burden of rotavirus. *J Infect Dis*. 2009;200 Suppl 1:S140–146.
14. Ito H, Otabe O, Katsumi Y, et al. The incidence and direct medical cost of hospitalization due to rotavirus gastroenteritis in Kyoto, Japan, as estimated from a retrospective

hospital study. *Vaccine*. 2011;29:7807–7810.

15. Nakagomi T, Chang BR, Nakagomi O. Rotavirus hospitalization and molecular epidemiology in northern Japan, 1987-1996. *Vaccine*. 2009;27 Suppl 5:F93–96.
16. Hiramoto I, Nakagomi T, Nakagomi O. Population-based estimates of the cumulative risk of hospitalization potentially associated with rotavirus diarrhea among children living in two cities in Akita Prefecture, Japan. *Jpn J Infect Dis*. 2005;58:73–77.
17. Kinoshita S, Noguchi A, Miura S, et al. A retrospective, hospital-based study to determine the incidence of rotavirus hospitalizations among children less than 5 years of age over a 10-year period (2001-2011) in Akita prefecture, Japan. *Jpn J Infect Dis*. 2014;67:464–468.
18. Kamiya H, Nakano T, Kamiya H, et al. Rotavirus-associated acute gastroenteritis hospitalizations among Japanese children aged <5 years: active rotavirus surveillance in Mie Prefecture, Japan. *Jpn J Infect Dis*. 2011;64:482–487.
19. Yokoo M, Miyagi Y, Nakagomi O. [A questionnaire-based surveys on the risk for hospitalization due to rotavirus gastroenteritis and the attitude towards rotavirus vaccine among caregivers and pediatricians]. *Clinical Virology*. 2009;37:211–223. [in Japanese]
20. Noguchi A, Ito H, Miura S, et al. Regional variations in the incidence of rotavirus hospitalization in children living in defined regions of Akita and Kyoto prefectures, Japan. *Jpn J Infect Dis*. 2017;70:167–170.
21. Tajiri H, Takeuchi Y, Takano T, et al. The burden of rotavirus gastroenteritis and hospital-acquired rotavirus gastroenteritis among children aged less than 6 years in Japan: a retrospective, multicenter epidemiological survey. *BMC Pediatr*. 2013;13:83.
22. Moroka K. Mild diarrhea and convulsions. *Pediatrics of Japan*. 1982;23:131–137. [in Japanese]
23. Takashima S, Yanai M. [A 19-year clinical investigation of inpatients with rotavirus gastroenteritis at a community hospital]. *The Journal of Pediatric Infectious Disease and Immunology*. 2018;30:204–211. [in Japanese]
24. Takeuchi S, Nishimura N, Kawaguchi M, et al. [Investigation of cases of hospitalization due to rotavirus gastroenteritis for the 2012 fiscal year]. *The Journal of Pediatric Infectious Disease and Immunology*. 2013;25:439–445. [in Japanese]
25. Ono H, Watanabe T, Tajima I, et al. [Clinical Features of 125 Children Hospitalized with Rotavirus Enteritis in Past 4 years]. *Journal of Iwata City Hospital*. 2013;14:5–7. [in Japanese]
26. Ogita J, Kurosaki T, Kubota H, et al. [Acute gastroenteritis in children in the 2004/2005 winter season: comparison of Rotavirus infection and Norovirus infection]. *The Journal of Pediatric Infectious Disease and Immunology*. 2006;18:365–370. [in Japanese]
27. Mizuguchi M. [Nationwide survey of acute encephalopathy. Research Report on Research Project for Overcoming Intractable Diseases]. Available at:

http://www.development.m.u-tokyo.ac.jp/Acute%20Encephalopathy/H22_AcuteEncephalopathy.pdf. Accessed March 13, 2020. [in Japanese]

28. Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev*. 2012;34:337–343.
29. Kawamura Y, Ohashi M, Ihira M, et al. Nationwide survey of rotavirus-associated encephalopathy and sudden unexpected death in Japan. *Brain Dev*. 2014;36:601–607.
30. Morishima T. Infantile viral encephalitis and encephalopathy in Japan. *Virus*. 2009;59:59–66. [in Japanese]
31. Ito H, Kawakatsu H, Yoshioka H, et al. [Examination of rotavirus vaccine introduction effect in Kyoto Prefecture]. *The Journal of the Kyoto Medical Association*. 2015;62:89–95. [in Japanese]
32. Goto S, Nosaka N, Yorifuji T, et al. Epidemiology of Pediatric Acute Encephalitis/Encephalopathy in Japan. *Acta Med Okayama*. 2018;72:351–357.
33. National Institute of Infectious Diseases. [Special feature: Rotavirus. September 2004-August 2019/ Infectious Agents Surveillance Report]. Available at: https://www.niid.go.jp/niid/ja/rotavirs-m/rotavirs-iasrtpc/9266-478t.html. Accessed March 13, 2020. [in Japanese]
34. Hattori F, Kawamura Y, Kawada JI, et al. Survey of rotavirus-associated severe complications in Aichi Prefecture. *Pediatr Int*. 2018;60:259–263.
35. Yoshida S, Hashimoto H, Narabayashi S, et al. [Current status and measures of rotavirus nosocomial infection in general pediatric wards]. *Japanese Journal of Pediatrics*. 2004;57:379–384. [in Japanese]
36. Nishimura A, Shibazaki Y, Kano S, et al. [Evaluation of hospital-acquired infection among noro and rota viral enteritis admissioned to our department of pediatrics]. *Japanese Journal of Pediatrics*. 2013;66:457–464. [in Japanese]
37. Takano T, Tajiri H, Kimura S. [Examination of mixed and nosocomial infections in hospitalized cases of infant norovirus enteritis and rotavirus enteritis]. *Japanese Journal of Pediatric Gastroenterology, Hepatology and Nutrition*. 2013;27:67. [in Japanese]
38. Parashar UD, Gibson CJ, Bresee JS, et al. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis*. 2006;12:304–306.
39. Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. 2010;375:1969–1987.
40. Kawai K, O'Brien MA, Goveia MG, et al. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. *Vaccine*. 2012;30:1244–1254.
41. Masumura C. [Table: Deaths by age group, gender, and cause] (2013). In: Japan Child and Family Research Institute, eds. *Almanac of Data on Japanese Children 2015*. KTC Central Publishing; 2015:118–121. [in Japanese]
42. Parashar UD, Hummelman EG, Bresee JS, et al. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis*. 2003;9:565–572.
43. Ushijima H, Ishida S. [Rotavirus vaccine]. *Japanese Journal of Clinical Medicine*. 2008;66:1977–1983. [in Japanese]

44. Japanese Ministry of Health, Labor and Welfare. [Demographic survey: Demographic statistics, Number of confirmed numbers, Storage statistics table (non-report table), Cause of death. e-Stat: Portal Site of Official Statistics of Japan]. Available at: https://www.e-stat.go.jp/dbview?sid=0003215611. Accessed March 13, 2020. [in Japanese]
45. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354:11–22.
46. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354:23–33.
47. Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med*. 2011;364:2283–2292.
48. Buttery JP, Danchin MH, Lee KJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011;29:3061–3066.
49. Payne DC, Baggs J, Klein NP, et al. Does preventing rotavirus infections through vaccination also protect against naturally occurring intussusception over time? *Clin Infect Dis*. 2015;60:163–164.
50. Clark AD, Hasso-Agopsowicz M, Kraus MW, et al. Update on the global epidemiology of intussusception: a systematic review of incidence rates, age distributions and case-fatality ratios among children aged <5 years, before the introduction of rotavirus vaccination. *Int J Epidemiol*. 2019;48:1316–1326.
51. Takeuchi M, Osamura T, Yasunaga H, et al. Intussusception among Japanese children: an epidemiologic study using an administrative database. *BMC Pediatr*. 2012;12:36.
52. Japanese Ministry of Health, Labor and Welfare. [Examination of the relationship between rotavirus vaccine and intussusception in Japan]. Available at: https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000207078_1.pdf. Accessed March 13, 2020. [in Japanese]
53. Miura M, Sato K, Muto H, et al. Intussusception in Japanese infants: Analysis of health insurance claims database. *OJPed*. 2013;3:311–316.
54. Noguchi A, Nakagomi T, Kimura S, et al. Incidence of intussusception as studied from a hospital-based retrospective survey over a 10-year period (2001-2010) in Akita Prefecture, Japan. *Jpn J Infect Dis*. 2012;65:301–305.
55. Nakagomi T, Takahashi Y, Arisawa K, et al. A high incidence of intussusception in Japan as studied in a sentinel hospital over a 25-year period (1978-2002). *Epidemiol Infect*. 2006;134:57–61.
56. Sunagawa T, Kamiya H, Kawano Y, et al. [Frequency of intussusception before rotavirus vaccine introduction in Japan (provisional results). Infectious Agents Surveillance Report]. Available at: https://www.niid.go.jp/niid/ja/iasr-sp/2261-related-articles/related-articles-409/4485-dj4098.html. Accessed March 13, 2020. [in Japanese]
57. Bauchau V, Van Holle L, Mahaux O, et al. Post-marketing monitoring of intussusception after rotavirus vaccination in Japan. *Pharmacoepidemiol Drug Saf*. 2015;24:765–

770.

58. Japanese Ministry of Health, Labor and Welfare. [About "Efficacy of rotavirus vaccine"]. Available at: https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000207162_1.pdf. Accessed March 13, 2020. [in Japanese]
59. Ikeda T. [Research guideline for evaluating the cost-effectiveness of vaccination. Japanese Ministry of Health, Labor and Welfare]. Available at: https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000184902_1.pdf. Accessed March 13, 2020. [in Japanese]
60. Brisson M, Sénécal M, Drolet M, et al. Health-related quality of life lost to rotavirus-associated gastroenteritis in children and their parents: a Canadian prospective study. *Pediatr Infect Dis J*. 2010;29:73–75.
61. Martin A, Cottrell S, Standaert B. Estimating utility scores in young children with acute rotavirus gastroenteritis in the UK. *J Med Econ*. 2008;11:471–484.
62. Iwata S, Ishiwada N, Sakata H, et al. [Burden of illness of bacterial meningitis and bacteremia caused by *Streptococcus pneumoniae* in children.] *Japanese Journal of Pediatrics*. 2008;61:2206–2220. [in Japanese]
63. Kawamura Y, Yoshikawa T. [Complications which one should be careful about, Central neurological complications caused by rotavirus infection]. *Japanese Journal of Medicine and Pharmaceutical Science*. 2016;73:265–20. [in Japanese]
64. Hoshi SL, Kondo M, Okubo I. Economic evaluation of vaccination programme of 7-valent pneumococcal conjugate vaccine to the birth cohort in Japan. *Vaccine*. 2012 May 9;30:3320–3328.
65. Bucher BT, Hall BL, Warner BW, et al. Intussusception in children: cost-effectiveness of ultrasound vs diagnostic contrast enema. *J Pediatr Surg*. 2011;46:1099–1105.
66. Tsevat J, Cook EF, Green ML, et al. Health values of the seriously ill. SUPPORT investigators. *Ann Intern Med*. 1995;122:514–520.
67. Nishimura S, Ushijima H. [Rotavirus vaccine –Examination from economic burden–]. *Pediatrics of Japan*. 1999;40:1337–1341. [in Japanese]
68. Kashiwagi Y. [Rota virus encephalopathy]. *Clinical Virology*. 2017;45:299–309. [in Japanese]
69. Bass DM. Rotaviruses, Caliciviruses, and Astroviruses. In Kliegman, St Geme ed. *Nelson Textbook of Pediatrics*. 21st ed.: Elsevier; 2020:1745–1747.
70. Rotavirus Infections. In *Red Book: 2018-2021 Report of the Committee on Infectious Diseases*, 31st ed.: American Academy of Pediatrics; 2018:700–704.
71. Nishimura S, Kito T, Nakaya S, et al. [Economics of rotavirus infection; No.1 a study in Manazuru City]. *The Journal of Pediatric Infectious Disease and Immunology*. 1999;11:369–372. [in Japanese]
72. Kimura T, Okabe N. Passive surveillance of rotavirus gastroenteritis-associated hospitalization using nationwide administrative databases in Japan. *J Infect Chemother*. 2019;25:175–181.

73. Kurosawa T, Yatagawa T, Ikemoto H, et al. [Clinical Features of Rotavirus Acute Gastroenteritis in Children: Influence and Efficacy of Vaccination and Comparison with Other Acute Gastroenteritis. *Teikyo Medical Journal*. 2019;42:173–184]. [in Japanese]
74. Japanese Ministry of Health, Labor and Welfare. [Estimated Number of Discharged Patients, Length of Stay in Hospital, Basic Injury and Disease Classification. e-Stat: Portal Site of Official Statistics of Japan]. Available at: https://www.e-stat.go.jp/stat-search/file-download?statInfId=000031790802&fileKind=1. Accessed March 13, 2020. [in Japanese]
75. Bruijning-Verhagen P, Quach C, Bonten M. Nosocomial rotavirus infections: a meta-analysis. *Pediatrics*. 2012;129:e1011–1019.
76. Sakiyama H, Jo A, Umemoto S, et al. [Cumulative Vaccination Coverage of Japanese Children Based on the National Surveys in 2017 and 2018]. *The Journal of Ambulatory and General Pediatrics*. 2019;22:462–470. [in Japanese]
77. Onogi K, Kameda T, Kubota K, et al. [Six-year vaccination status based on the questionnaire for new children in nursery schools in Kawasaki City]. *Japanese Journal of Well-being for Nursery-schoolers*. 2020;26:36–39. [in Japanese]
78. Kurosawa T, Watanabe H, Takahashi K. [Estimating effectiveness of rotavirus vaccines including herd immunity in Japan]. *Journal of the Kawasaki city pediatric society*. 2020 (in press). [in Japanese]
79. Mizuguchi M. [Nationwide survey of acute encephalopathy (2nd). Intractable Disease Policy Research Project]. Available at: http://www.development.m.u-tokyo.ac.jp/Acute%20Encephalopathy/20190329/Acute%20encephalopathy_2nd%20surveryR.pdf. Accessed March 13, 2020. [in Japanese]
80. Nomoto H, Konishi N, Moriya M, et al. [Economic effects of rotavirus gastroenteritis on families of affected infants]. *J Chugoku Rosai Hosp*. 2014;23:6-9. [in Japanese]
81. Japanese Ministry of Health, Labor and Welfare. [Overview of the Survey on Wage Structure Basic Statistics 2018. Japanese Ministry of Health, Labor and Welfare]. Available at: https://www.mhlw.go.jp/toukei/itiran/roudou/chingin/kouzou/z2018/dl/02.pdf. Accessed March 13, 2020. [in Japanese]