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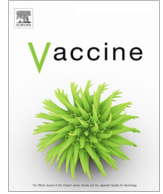
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Cost-effectiveness analysis of the implementation of a National Immunization Program for rotavirus vaccination in a country with a low rotavirus gastroenteritis-related mortality: A South Korean study



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ABSTRACT

Rotavirus is a leading cause of severe gastroenteritis among children younger than 5 years in South Korea. Two rotavirus vaccines (RVs), pentavalent human-bovine reassortant vaccine (Rotateq[®]; RV5) and attenuated human strain originated monovalent vaccine (Rotarix[®]; RV1), have been available for voluntary vaccination using out-of-pocket payment since 2007 and 2008, respectively. Yet, RVs are not included in the National Immunization Program (NIP), partly because of the low associated mortality rate. We assessed the cost-effectiveness of RVs to assist the evidence-based decision-making process for NIP implementation in South Korea. Using a transparent age-structured static cohort model, we simulated the experience of ten annual birth cohorts of South Korean children from 2018 to 2027. Model inputs included rotavirus gastroenteritis (RVGE) incidence and mortality rates, RVGE treatment costs, vaccine coverage and timeliness, and vaccine effectiveness and price. The incremental costs of including RVs in the NIP compared to no vaccination were 59,662,738 USD and 152,444,379 USD for RV1 and RV5, respectively. The introduction of RV1 and RV5 can prevent 4799 disability-adjusted life years (DALYs) and 5068 DALYs. From the societal perspective, the incremental cost-effectiveness ratios (ICERs) for adopting RV into the NIP versus no vaccination were 12,432 USD per DALY averted for RV1 and 30,081 USD per DALY averted for RV 5. The weighted average for the ICERs of the two vaccines computed using the market share of each vaccine in the current voluntary use as a weight, was 21,698 USD per DALY averted. The estimated ICER was below 1 × gross domestic product per capita (30,000 USD), which has been a commonly used willingness-to-pay threshold for health care technology assessment in South Korea, suggesting that introducing RVs into the NIP would be cost-effective.

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Abbreviations: ADE, adverse event; DTP, diphtheria-tetanus-pertussis; HIRA, Health Insurance and Review and Assessment Service; KCDC, Korea Centers for Disease Control and Prevention; KOSIS, Korean Statistical Information Service; NHIS, National Health Insurance Service; NIP, National Immunization Program; RR, relative risk; RV, rotavirus vaccine; RV1, attenuated human strain originated monovalent vaccine (Rotarix[®]); RV5, pentavalent human-bovine reassortant vaccine (Rotateq[®]); RVGE, rotavirus gastroenteritis; USD, United States dollars; GDP, gross domestic product.

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1. Introduction

Rotavirus is a leading cause of severe gastroenteritis among children <5 years of age, accounting for 111 million gastroenteritis cases, 25 million outpatient visits, 2 million hospitalizations, and 216,000 deaths, worldwide, annually [1–4]. Almost all children have an episode of rotavirus gastroenteritis (RVGE) at least once before their fifth birthday [5]. Rotavirus is transmitted via the

feco-oral route and infects intestinal cells, resulting in the clinical presentation of vomiting, fever, severe diarrhea, and dehydration.

While mortality associated with RVGE is rare in high-income countries, the incidence of RVGE is similar in both high- and low-income countries, regardless of hygiene standards [3,6]. Before the introduction of rotavirus vaccines (RVs) in South Korea, the annual incidence of rotavirus infection was 56.9/1000 children under 5 years old and that of hospitalizations due to rotavirus infection was 11.6/1000 children from 2002 to 2004 [7]. The inpatient and outpatient costs due to rotavirus infection present a substantial economic burden. According to Yang et al., the direct cost of RVGE treatment in Korea was approximately 11 million US dollars (USD; 1 USD approximately equals 1100 Korean won), of which 8 million USD was spent on inpatient care and 3 million USD on outpatient care in 2005 [8]. In 2013, another burden-of-disease study conducted in Korea by Kang et al. showed that the average length of stay per hospitalization in the case of RVGE was 5.33 days and that the cost per hospitalization was 1344 USD including medical costs and indirect costs such as the loss of productivity among caregivers [9].

RVs can prevent RVGE and the severe dehydration from the diarrhea it causes [10]. In high-income settings, rotavirus vaccination has demonstrated high and durable protection against episodes of severe RVGE [11]. In 2009, the World Health Organization (WHO) recommended the inclusion of RVs into the National Immunization Program (NIP) of all countries [12]. As of October 2017, 93 countries, including both high- and low-income countries, had included rotavirus vaccines in their NIPs [13].

In Korea, two oral live rotavirus vaccines, the pentavalent human-bovine reassortant vaccine RotaTeq® (MSD Korea LLC.; RV5) and attenuated human strain originated monovalent vaccine Rotarix® (GlaxoSmithKline Ltd.; RV1), were approved for use in 2007 and 2008, respectively. RV5 is administered via a 3-dose schedule in infants aged 6 weeks to 32 weeks (i.e., at 2, 4, and 6 months), while RV1 is administered via a 2-dose schedule in infants aged 6 weeks to 24 weeks (i.e., at 2 and 4 months). In 2016, the vaccination rate of RVs reached as high as 84.5% with out-of-pocket spending in the private market, but a substantial proportion of children remained unvaccinated [14]. Thus, the Korean government considered including RVs into the NIP, so that all infants would receive RVs without out-of-pocket burden.

The aim of this analysis was to evaluate the cost-effectiveness of making rotavirus vaccination available to all South Korean infants via the publicly funded South Korean NIP compared to no rotavirus vaccination. In addition to disease burden and vaccine efficacy, the cost-effectiveness of vaccination is crucial to NIP introduction. We expect that our study results would help inform policymaker's evidence-based decision-making regarding rotavirus vaccination implementation as part of the NIP in South Korea.

2. Materials and methods

2.1. Model overview

The Microsoft Excel-based UNIVAC model, a static decision analytic cohort model developed by the London School of Hygiene and Tropical Medicine (LSHTM) and the WHO Pan American Health Organization (PAHO) to support the economic evaluation of various vaccines worldwide [15,16], was used. The model estimates the expected number of episodes of non-severe RVGE, severe RVGE, and intussusception, a rare adverse event due to vaccination (Supplementary Fig. 1). Severe RVGE cases were those that required hospitalization, whereas non-severe RVGE cases were those that only required outpatient visits. The consequence of each health state is presented as “recovery” or “death.”

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2019.07.030>.

We simulated the experience of a number of hypothetical annual birth cohorts of Korean children from 2018 to 2027 following each birth cohort up to a maximum age of 5 years for disease events and costs, and over a lifetime for disability-adjusted life years (DALYs). The size of the birth cohort for each year was obtained from the Korea future population projection data by Statistics Korea [17]. The outcomes were: DALYs averted by the prevention of RVGE through vaccination; and incremental costs, i.e., the increased costs due to vaccination minus the RVGE treatment costs averted. The cost-effectiveness of vaccination was presented as the incremental cost-effectiveness ratio (ICER)—the incremental cost per DALY averted, with future costs and benefits discounted at 3% per year, to reflect the present values in 2018. All costs were estimated from the societal perspective, including costs borne by the government (e.g., facility and staff costs, drugs and diagnostics) and costs borne by families (e.g., travel and lost wages).

Two vaccines (RV1 and RV5) have been approved and are currently used on a voluntary basis in the private market in South Korea.

We calculated three ICERs:

1. Introduction of RV1 into the NIP, compared to no vaccination;
2. Introduction of RV5 into the NIP, compared to no vaccination; and,
3. Introduction of both RV1 and RV5 into the NIP, assuming that 47.5% of the vaccines delivered were RV1 and 52.5% were RV5. This was the market share reported in the 2016 Immunization Information Registry System by the Korea Centers for Disease Control and Prevention (KCDC) [14].

2.2. Model input parameters

As shown in Table 1, the key input parameters of the model included the baseline incidence of non-severe and severe RVGE before the introduction of the RV in Korea, vaccine effectiveness, incidence of intussusception, disability weights for RVGE, vaccination costs, and costs of illness for RVGE. We attempted to collect data for each parameter based on national evidence. For example, the epidemiologic and healthcare utilization characteristics associated with RVGE were investigated from National Health Insurance (NHI) claims data (NHIS-2017-1-293). The disability weights for RVGE were obtained from a local study [18]. We also made the critical assumption that the price of the vaccines offered to the government under the NIP would be equivalent to the prices currently offered in the private market, but assumed a price reduction consistent with the expected increase in the number of doses purchased. Where local data were unavailable, recent systematic reviews or evidence from other countries was used.

2.2.1. Epidemiologic characteristics of RVGE

The baseline epidemiologic and healthcare utilization characteristics associated with RVGE in children aged under 5 years were investigated in 2006, the year before RVs were introduced in Korea. Based on the 2006 NHI claims data, we determined the incidence rates of severe and non-severe RVGE. Each RVGE case was defined as that with the RVGE diagnostic code (i.e., A08.0), according to the International Classification of Diseases (ICD)-10, in the claims records. The incidence rates of both severe and non-severe RVGE cases were estimated in terms of episodes. To estimate the incidence of severe RVGE cases, we assessed outpatient visits two weeks before and after the hospitalization period in patients with a history of RVGE-related hospitalization. If outpatient visits were

Table 1
Input parameters of the model.

Parameters		Data values for the base case	Sources	
Epidemiology of RVGE				
Annual rate (per 100,000 children aged under 5 years)	Non-severe RVGE (No. of outpatient visits for RVGE)	2,639	Korea NHIS in 2006	
	Severe RVGE (No. of outpatient visits prior to or following hospitalization for RVGE)	230		
	Severe RVGE (No. of hospitalization for RVGE)	1,471		
	No. deaths due to RVGE	0.13	[19]	
Age distribution of all RVGE cases, (%)	<1 month	8.4	Korea NHIS in 2006	
	1 ≤ age < 2 months	4.0		
	2 ≤ age < 3 months	2.3		
	3 ≤ age < 6 months	6.0		
	6 months ≤ age < 1 year	18.3		
	1 ≤ age < 2 years	34.5		
	2 ≤ age < 3 years	15.2		
	3 ≤ age < 4 years	8.4		
	4 ≤ age < 5 years	2.9		
Vaccine effectiveness and adverse events				
Vaccine effectiveness	% reduction of RVGE	RV1 1 dose	77	[20] (values for low mortality countries)
		2 doses	82	
		RV5 1 dose	73	
		2 doses	82	
		3 doses	88	
		Vaccine coverage (%)	1 dose	
		2 doses	95.0–99.9	
		3 doses (only RV5)	95.0–99.9	
Intussusception as ADE (Annual rate per 100,000 people aged under 5 years, n)	Hospitalization, incidence rate		112	Korea NHIS in 2006
		Mortality	0.17	
	RR for intussusception within 3 weeks following vaccination	RV1 1 dose	5.4	[19]
		2 doses	1.8	[25]
		RV5 1 dose	5.5	
		2 doses	1.7	
Utility				
Percentage of healthy time lost while living with disease (%)	Non-severe RVGE	35.9	[18] (Mild diarrhea)	
	Severe RVGE	53.5	[18] (Moderate diarrhea)	
	Intussusception	79.3	[18] (Severe abdominopelvic problem)	
Average duration of illness (time spent living with disease in years)	Non-severe RVGE	0.009	Korea NHIS in 2006	
	Severe RVGE	0.022		
	Intussusception	0.009		
Costs (USD)				
Cost of treating RVGE	Non-severe RVGE (Average cost per outpatient visit for RVGE)	54.22	Korea NHIS in 2006	
	Severe RVGE (Average cost per outpatient visit prior to or following hospitalization for RVGE)	57.83		
	Severe RVGE (Average cost per hospitalization for RVGE)	2084.51		
Costs of treating ADE of vaccination	Average cost per hospitalization for intussusception	1286.66	Korea NHIS in 2006	
	Vaccination cost under the NIP	Confidential		
	Vaccine price per dose	Confidential		
	Vaccine administration cost per dose under NIP	16.91	KCDC	

ADE = adverse event. KCDC = Korea Centers for Disease Control and Prevention. KPIS = Korea Pharmaceutical Information Service. NHIS = National Health Insurance Service. NIP = National Immunization Program. RR = relative risk. RV1 = attenuated human strain originated monovalent vaccine (Rotarix®). RV5 = pentavalent human-bovine reasortant vaccine (Rotateq®). RVGE = rotavirus gastroenteritis. USD = US dollars
All costs are estimated from the societal perspective and presented in 2018 US dollars. An exchange rate of 1 USD to 1,100 Korean won is applied.

made in the two weeks before and after the hospitalization period, the visits were considered to be related to the hospitalization and were included in the same hospitalization-related episode. After excluding all hospitalization-related RVGE episodes, the incidence of non-severe RVGE cases was calculated as the number of outpatient episodes for RVGE treatment. If an RVGE outpatient visit was made within two weeks of the first RVGE outpatient visit, it was included in the same RVGE outpatient episode.

Meanwhile, when patients with gastroenteritis self-treat themselves without making hospital visits, healthcare services are not used; hence, as medical costs were incurred, these cases were not included in the model. However, the incidence rate of untreated RVGE was conceptually estimated based on the assumption that half of the actual RVGE cases involved use of healthcare services.

The mortality associated with RVGE was estimated from the 2006 National Statistics for Causes of Death in Korea among children younger than 5 years [19]. Since the mortality due to RVGE could not be distinguished, we considered the mortality due to diarrhea-related enteritis excluding serious diseases legally designated such as cholera, typhoid and paratyphoid fever, salmonellosis, other bacterial food poisoning. Therefore, the mortality rate due to RVGE was calculated as 0.13 per 100,000 children younger than 5 years as of 2006.

2.2.2. Vaccine effectiveness

To analyze the effectiveness of RVs, we used data from the systematic review by Jonesteller et al. [20], which provided meta-analysis results for both RV1 and RV5 based on literature comparing the incidence of RVGE between vaccinated and unvaccinated people in real-world settings [20]. Since the effectiveness of RVs

varies across countries depending on the all-cause mortality for children under age 5 years in a country, the meta-analysis results were presented separately for countries with low, medium, or high mortality. As the mortality in South Korea was within the lowest quartile, we applied the vaccine effectiveness of the countries in the lowest quartile: the percentage reduction in the incidence of RVGE after the completion of all the vaccination doses was 82% (95% confidence interval [CI]: 72–88) for RV1 and 88% (95% CI: 83–91) for RV5. The effectiveness of partial dosing was also applied in the model based on the partial dose estimates for each vaccine from the study conducted by Jonesteller et al. [20].

The clinical outcomes associated with the prevention of RVGE incidence were measured as DALYs averted. DALYs are calculated by multiplying disability weights by the duration of illness. The disability weights for non-severe and severe RVGE cases and intussusception cases were obtained from a local study conducted by Ock et al. [18], which were derived from mild diarrhea, moderate diarrhea and severe abdominal problems, respectively. The average duration of illness for non-severe RVGE, severe RVGE, and intussusception—denoting the time spent living with the disease in years—were estimated from NHI claims data using a combination of ICD-10 codes and hospitalization history.

2.2.3. Vaccination coverage

Since the rotavirus vaccination schedule, which is a 2-dose schedule at 2 and 4 months of age or a 3-dose schedule at 2, 4, and 6 months of age, is similar to that for diphtheria-tetanus-pertussis (DTP) vaccination, we assumed that the coverage rate for RVs under the NIP would be the same as that for DTP vaccines. Although the full DTP vaccination rate was reported to be 99.6% by the KCDC, we expected that the coverage rate of the RV in the first year of NIP implementation could not reach 99.6%; therefore, it was assumed to be 95.0% [21]. Then, we applied a gradual increase of 1% every year to reach a value of 99.9% in the sixth year of inclusion in the NIP. Since the delayed inoculation of the DTP vaccine was rare according to KCDC internal documents, we hypothesized that about 90% of rotavirus shots were inoculated on time.

2.2.4. Vaccine-related adverse events

Intussusception is a rare but life-threatening adverse event following rotavirus vaccination [22–24]. The mortality and hospitalization associated with intussusception due to rotavirus vaccination was incorporated in the analysis. To estimate the mortality related to intussusception after rotavirus vaccination, the mortality rate per 100,000 per year was defined as the mortality due to all-cause intussusception (ICD-10 code: K56 [paralytic ileus and intestinal obstruction without hernia]) from the 2006 National Statistics for Causes of Death in Korea [19] as the number of background cases expected. The mortality rate due to intussusception was estimated by multiplying the number of background cases by the relative risk (RR) of intussusception within 3 weeks following rotavirus vaccination. The RR was obtained from Rosillon et al. [25], who provided meta-analysis results from post-licensure observational studies conducted after rotavirus vaccination [25]. The RR (95% CI) was used as 5.4 (3.9–7.4) in dose 1 and 1.8 (1.3–2.5) in dose 2 for RV1, and for RV5 the RR (95% CI) was used as 5.5 (3.3–9.3) in dose 1 and 1.7 (1.1–2.6) in dose 2 or 3. The incidence of hospitalization due to intussusception following rotavirus vaccination was calculated by multiplying the RR by the number of background cases hospitalized with intussusception in the 2006 NHI claims data.

2.2.5. Vaccination costs

Vaccination costs include vaccine price and vaccine administration costs. The market price for RV1 and RV5 in 2016 was obtained from the Korea Pharmaceutical Information Service (KPIS) provided

by the Health Insurance Review and Assessment service. The vaccine price, as obtained from the KPIS, is the average value of prices declared by vaccine suppliers. There were no separate vaccine administration charges that patients paid, since the vaccine price was set to include administration costs. Since RV1 and RV5 are sold by different companies, and the KPIS considers detailed data on the price information of suppliers as confidential in Korea, we are not allowed to publish the price information in this manuscript.

Once RV is included in the NIP, the current average out-of-pocket market price of the vaccine (A) will reduce proportionately to the increase in the vaccine coverage (B%), as is the conventional practice in Korea's NIP. Thus, we used the reduced vaccine price ($A \times (100\% - B\%)$) as the base-case value for the NIP implementation arm in the model. For example, if the current average out-of-pocket market price of the vaccine (A) is 50.00 USD and the vaccine coverage will increase 10% points after the NIP implementation, the reduced vaccine price ($45.00 \text{ USD} = 50.00 \times (100\% - 10\%)$) was used in the model. In addition, following the “Regulation of vaccination on consignment,” we added a fixed service fee (16.91 USD) per vaccine administration, which is reimbursed to health-care providers, to cover vaccination costs under the NIP. Therefore, the single rotavirus vaccination cost after the NIP implementation is the total cost of the vaccine price and the administration cost ($61.91 \text{ USD} = 45.00 + 16.91$).

Treatment costs for vaccine-related adverse events were also included in the model as costs for hospitalization due to intussusception. From the NHI claims data, the average costs of hospitalization with the diagnosis of intussusception following the ICD-10 codes of K56.1 (intussusception), K38.8 (other specified diseases of the appendix), or K91.3 (post-procedural intestinal obstruction) were estimated.

2.2.6. Costs of illness

The costs of illness in treating RVGE were derived from the NHI claims database in 2006. All the estimated costs were converted to the present value in 2018. The NHI is a mandatory universal health insurance in South Korea and covers the entire population. All claims records with an RVGE diagnosis according to ICD-10 code A08.0 were defined as treated RVGE cases. The average costs calculated from outpatient visits were used as non-severe RVGE costs in the model. The average costs for outpatient visits related to hospitalization and average costs for hospitalization were used as severe RVGE costs in the model. Societal perspectives included not only reimbursement expenses but also out-of-pocket expenses, transportation costs, and caregivers' costs derived from various sources.

2.3. Modeled analysis

2.3.1. Base-case analysis

For the base case, the cost-effectiveness was assessed as incremental costs per DALY averted, as presented below:

$$\text{ICER} = (\text{Cost}_{\text{NIP}} - \text{Cost}_{\text{No vaccination}}) / (\text{DALY}_{\text{NIP}} - \text{DALY}_{\text{No vaccination}})$$

where

ICER: incremental cost-effectiveness ratio
 NIP: National Immunization Program
 DALY: disability-adjusted life years

The ICER is a resulting value of the cost-effectiveness analysis and an index that measures the additional cost per incremental unit of utility required compared to the alternative. ‘DALY’, which has been used widely in existing cost-effectiveness studies on government-funded health projects such as the NIP, was employed in this study as the measurement unit of utility [26]. DALYs are cal-

culated on the basis of disutility (i.e., disability weights) and the number of days lived with the disease in years, with 'ICER' representing the incremental costs required to prevent 1 DALY.

2.3.2. Sensitivity analyses

The robustness of the ICER was assessed using univariate sensitivity analyses by varying the base-case values of selected variables. Healthcare costs associated with RVGE treatment, disability weights for RVGE, vaccine price, vaccine effectiveness, annual discount rate, RVGE mortality, and vaccination rate were selected for the univariate sensitivity analysis (Table 2). The lower healthcare cost values were derived from the RVGE cases, defined as claims records with a primary diagnosis of RVGE instead of all diagnoses of RVGE defined for base cases. Assuming that the uncaptured healthcare cost was approximately 10% of the base-case value, the upper value of the healthcare costs was estimated by multiplying the base-case value by 1.1. The lower values of the disability weights were obtained from the Global Burden of Disease (GBD) study: 0.188 for non-severe RVGE (i.e., moderate diarrhea) and 0.247 for severe RVGE (i.e., severe diarrhea) [27]. With regards to vaccine price, two premises, one of which assumes that the current average market price of the vaccine (A) is maintained after its inclusion in the NIP and the other which assumes that the minimum current market price of the vaccine (C) will reduce proportionately to the increase in the vaccine coverage (B %) ($C \times (100\% - B\%)$) after the inclusion in the NIP, were used for the upper and lower values, respectively. For example, if the current average market price of the vaccine (A) is 50.00 USD and the minimum market price (C) is assumed to be 40.00 USD and the vaccine coverage rate is expected to increase by 10% after the NIP, the upper value would be 50.00 USD and the lower value 36.00 USD ($40.00 \text{ USD} \times (100\% - 10\%)$).

For RV effectiveness, CIs from the study conducted by Jonesteller et al. were used as the lower and upper values [20]. To take into account the indirect effect of rotavirus vaccination on herd

immunity, the ICER was additionally derived by multiplying the effectiveness of each vaccine by 1.2 and 1.28. The multiplier '1.2' was the value assumed to estimate the herd effect in previous rotavirus cost-effectiveness studies using the UNIVAC (or TRIVAC) model [28], and '1.28' was derived from a study conducted by Pollard, in which 22% of the total RV effect was related to herd immunity ($1.28 = 1/(1-0.22)$) [29].

The annual discount rates were assumed to be 1% and 5% for the sensitivity analysis. In the given data, there were difficulties associated with specifying the cause of death as RVGE. Therefore, we considered RVGE cases without death for the lower value and all cases of gastroenteritis-related death for the upper value, which was reported by the Korean Statistical Information Service as 0.38 deaths per 100,000 per year among those aged under 5 years [19]. As RVs and DTP vaccines are usually administered simultaneously in Korea, the reported minimum and maximum DTP vaccine coverage values were used as the lower and upper RV coverage values, respectively [21]. Furthermore, the variables found to be sensitive in the univariate sensitivity analysis were combined for use in the multivariate sensitivity analysis employing scenarios. Scenario analysis predicts outcomes in a fictional environment in which a multitude of variables vary at the same time. A total of six scenarios were analyzed, scenario 1 being the combination of only variables which have a positive impact on the ICER, and scenario 6 including variables with a negative impact on the ICER only. The healthcare costs of RVGE and vaccine effectiveness were set as the maximum while the price of the vaccines was set as the minimum under scenario 1; the opposite was applied to scenario 6.

3. Results

3.1. Base-case analysis results

The baseline disease burden due to RVGE in 2006, when neither RV1 nor RV5 was available in South Korea, was 7468 DALYs. The

Table 2
Variables for the sensitivity analysis.

Variables		Lower value	Upper value	Sources
Healthcare costs (USD)	Non-severe RVGE, per outpatient visit	54.06	59.64	Korea NHIS for lower values Assumptions for upper values ($1.1 \times$ base case values)
	Severe RVGE, per outpatient visit	55.97	63.61	
	Severe RVGE, per hospitalization	1,359.70	2,292.97	
Percentage of healthy time lost whilst living with disease (%)	Non-severe RVGE, per outpatient visit	18.8	53.5	[27] for lower values [18] for upper values (Severe diarrhea)
	Severe RVGE, per outpatient visit	24.7	61.4	
	Severe RVGE, per hospitalization	32.4	79.3	
Vaccine price per dose	RV1	Confidential		KPIS
	RV5			
Effectiveness per vaccine dose (% reduction)	RV1	1 dose	73	[20] (Low mortality countries)
		2 doses	78	
	RV5	1 dose	68	[20] (Low mortality countries)
		2 doses	77	
		3 doses	83	
Annual discount rate		1.0%	5.0%	Assumption
RVGE, mortality (per 100,000 children under age 5 years, n)		0	0.38	[19]
Vaccine coverage (%)	1 dose	95.0–97.0	100.0	[21] DTP vaccine coverage from KCDC
	2 dose	95.0–97.0	100.0	
	3 doses (RV5 only)	95.0–97.0	100.0	

DTP = diphtheria-tetanus-pertussis. KCDC = Korea Centers for Disease Control and Prevention. KPIS = Korea Pharmaceutical Information Service. NHIS = National Health Insurance Service. RV1 = attenuated human strain originated monovalent vaccine (Rotarix®). RV5 = pentavalent human-bovine reassortant vaccine (Rotateq®). RVGE = rotavirus gastroenteritis. USD = US dollars

All costs are estimated from the societal perspective and presented in 2018 US dollars. An exchange rate of 1 USD to 1,100 Korean won is applied.

Table 3
Cost-effectiveness analysis result of including rotavirus vaccines into the NIP in South Korea (Base case).

Variable	No vaccination	NIP	
		RV1	RV5
<i>Costs (USD)</i>			
Cost of illness in treating RVGE	591,450,787	195,264,131	173,123,891
Cost of illness averted by the NIP (1)	–	–396,186,657	–418,326,897
Vaccination costs of the NIP (2)	–	455,849,395	570,771,276
Incremental costs of the NIP vs. no vaccination, (1)+(2)	–	59,662,738	152,444,379
<i>Effectiveness</i>			
DALYs	7,468	2,669	2,400
Incremental effectiveness (DALY averted) of NIP vs. no vaccination	–	–4799	–5068
ICER (Inc. cost per DALY averted)	–	12,432	30,081
	–	21,698*	

DALY = disability-adjusted life years. ICER = incremental cost-effectiveness ratio. NIP = National Immunization Program. RV1 = attenuated human strain originated monovalent vaccine (Rotarix®). RV5 = pentavalent human-bovine reassortant vaccine (Rotateq®). RVGE = rotavirus gastroenteritis. USD = US dollars. All costs are estimated from the societal perspective and presented in 2018 US dollars. An exchange rate of 1 USD to 1,100 Korean won is applied.

* The final ICER was calculated as the weighted average of the ICERs of RV1 and RV5, using the estimated proportions of children fully immunized with each vaccine as weights (47.5% and 52.5%) from the 2016 birth cohort registry in South Korea.

modeled simulation applying the effectiveness of RV1 and RV5 under the scenario in which the vaccines are adopted by the NIP resulted in estimated RVGE burdens of 2669 and 2400 DALYs, respectively, indicating an incremental effectiveness of 4799 DALYs with RV1 and 5068 DALYs with RV5.

From a societal perspective, the inclusion of RV1 in the NIP would entail operational costs of around 456 million USD, and avert the cost of RVGE treatment by 396 million USD over 10 years, resulting in an incremental cost of about 60 million USD. Similarly, the inclusion of RV5 would accrue operational costs of 571 million USD and avert the cost of RVGE treatment by 418 million USD, resulting in an incremental cost of about 152 million USD (Table 3).

Cost-effectiveness analyses showed that approximately 12,432 USD would be required to prevent 1 DALY under the inclusion of RV1 in the NIP. This value was derived by dividing the incremental cost of 60 million USD by the incremental effectiveness of the 4799 DALYs averted. In the case of the inclusion of RV5, the ICER was found to be about 30,081 USD per DALY averted, calculated by dividing the incremental cost of 152 million USD by the incremental effectiveness of 5068 DALYs (Table 3).

The final ICER was calculated as the weighted average of the ICERs of RV1 and RV5. The resulting ICER was 21,698 USD per DALY averted if both types of RVs were to be included in the NIP. Since it is smaller than $1 \times \text{GDP}$ per capita in Korea (29,742 USD in 2017) [30] we interpreted that including RV1 and RV5 in the NIP in Korea could be cost-effective. One to two GDP per capita was used as the ICER threshold or willingness-to-pay (WTP) threshold in this study, which is commonly used for health care technology assessment in South Korea [31,32].

3.2. Sensitivity analysis results

We interpreted the sensitivity analysis results based on the ICER threshold. If the ICER calculated using the lower or upper value instead of the base-case value of a variable exceeded the ICER threshold, we considered that the cost-effectiveness of the vaccine is sensitive to the variable, and the uncertainty of the variable is crucial to reach a robust conclusion on vaccine cost-effectiveness.

Univariate sensitivity analysis of the cost-effectiveness of RV1 in the case of its inclusion in the NIP showed an ICER of 3929 USD per DALY averted when the incidence of non-severe RVGE in 2006 was estimated based on the literature. The ICER of RV1 appeared to be sensitive to healthcare costs, disability weights, and vaccine price because the calculated ICERs using the lower and upper values for each variable showed a wide range. However,

none of these variables generated ICERs greater than $2 \times \text{GDP}$ (Fig. 1).

With respect to the univariate sensitivity analysis for RV5, the estimation of non-severe RVGE based on the result of previous studies resulted in an ICER of 14,373 USD/DALY averted, which remains within the $1 \times \text{GDP}$ limit. The ICER of RV5 responded sensitively to vaccine price per dose, healthcare costs, and disability weights, with values greater than $1 \times \text{GDP}$ or $2 \times \text{GDP}$ (Fig. 1).

When herd immunity was taken into account, the inclusion of RV1 in the NIP was analyzed as having a cost-saving effect. In the scenario analysis, the ICER of RV1 ranged from cost-saving to 58,169 USD/DALY averted. The ICER of RV5 was found to be 16,130 USD/DALY averted when herd immunity was considered. In the scenario analysis, the ICER of RV5 ranged from 12,617 to 79,462 USD/DALY averted (Tables 4 and 5).

4. Discussion

To the best of our knowledge, this is the first study to analyze the cost-effectiveness of the two RVs currently used in South Korea, if they were to be included in the NIP. The base-case analysis results revealed that the inclusion of the two vaccines would generate ICERs lower than $1 \times \text{GDP}$ per capita—the WTP threshold which is customary acceptable in South Korea. Thus, we can conclude that the adoption of the two RVs into the NIP would be cost-effective. Univariate sensitivity analyses demonstrated that the ICER was insensitive to vaccine effectiveness, RVGE mortality, vaccine coverage rate, and annual discount rate. However, the ICER was sensitive to the uncertainty of the following variables: RVGE incidence rate, vaccine price per dose, disability weights for severe and non-severe RVGE, and the associated healthcare costs. Therefore, future studies should improve upon the uncertainty of those variables for a more robust economic evaluation of rotavirus vaccination.

In our analysis, we attempted to derive a valid estimation for the cost-effectiveness of RVs utilizing local real-world evidence. Model parameters, such as RVGE incidence, duration of an RVGE episode, and the healthcare costs associated with RVGE treatment, were obtained from NHI claims records, and are, therefore, nationally representative data reflecting healthcare utilization patterns in real practice settings. To quantify the localized clinical outcomes resulting from the adoption of RVs by the NIP in Korea, we used disability weights for RVGE derived from the Korean population instead of those from the GBD study. Most of the remaining model parameters, such as vaccination coverage and vaccine price, were

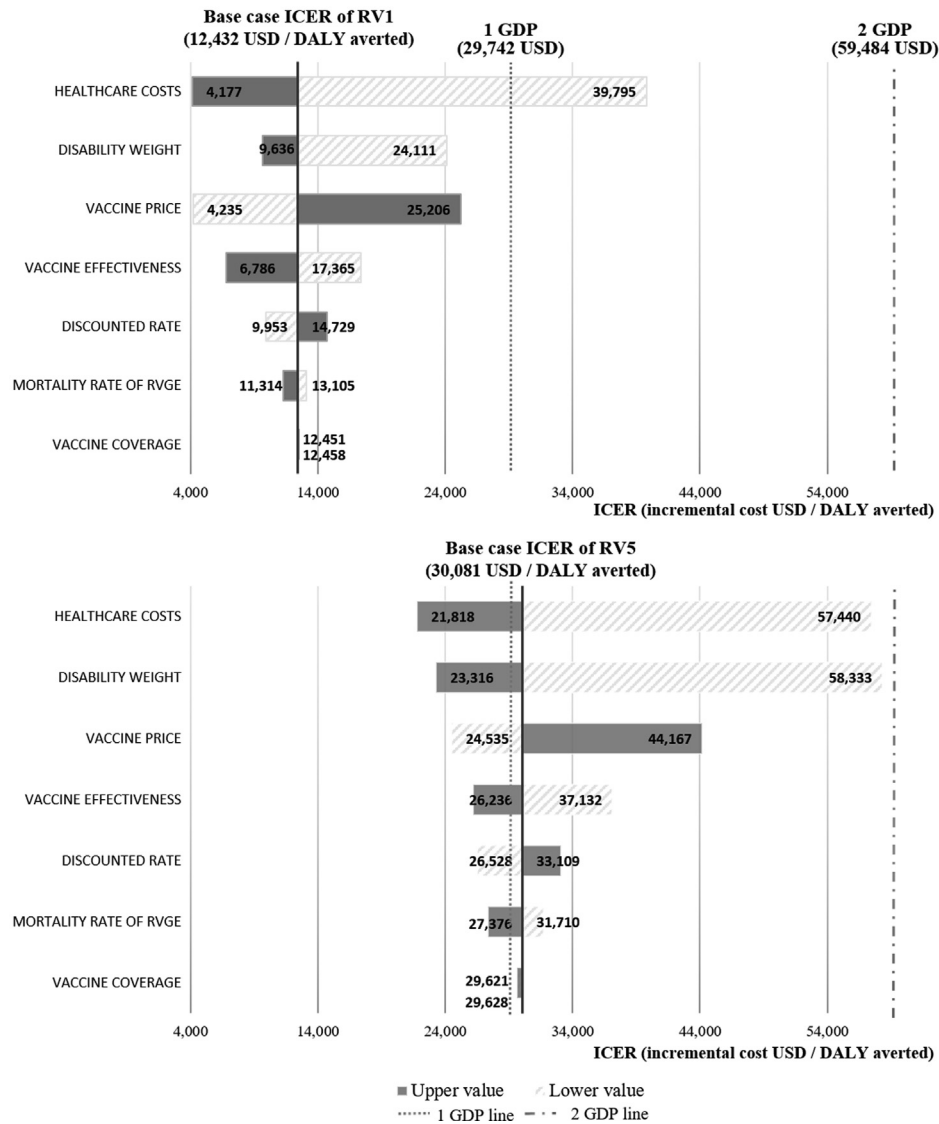


Fig. 1. Tornado diagrams for the univariate analysis of RV1 and RV5 versus no vaccination, in terms of the incremental cost-effectiveness ratio. DALY, disability-adjusted life years; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; RV1, attenuated human strain originated monovalent vaccine (Rotarix®); RV5, pentavalent human-bovine reassortant vaccine (Rotateq®); RVGE, rotavirus gastroenteritis; USD, United States dollars.

Table 4
Cost-effectiveness of RV1 and RV5 reflecting herd immunity in South Korea.

Variable		RV1	RV5
Effectiveness reflecting herd immunity (% reduction)	1 dose	93.4 (Assumption 1)	85.0 (Assumptions 1 & 2)
		95.0 (Assumption 2)	
	2 doses	98.4 (Assumption 1)	94.0 (Assumptions 1 & 2)
		100.0 (Assumption 2)	
ICER (Inc. cost per DALY averted)	3 doses (RV5 only)	–	100.0 (Assumptions 1 & 2)
		Cost-saving	16,130

DALY = disability-adjusted life years. ICER = incremental cost-effectiveness ratio. RV1 = attenuated human strain originated monovalent vaccine (Rotarix®). RV5 = pentavalent human-bovine reassortant vaccine (Rotateq®). RVGE = rotavirus gastroenteritis. USD = US dollars. All costs are estimated from the societal perspective and presented in 2018 US dollars. An exchange rate of 1 USD to 1,100 Korean won is applied. Assumption 1 implies the effectiveness of the rotavirus vaccine multiplied by 1.2 to include herd immunity. Assumption 2 implies the effectiveness of the rotavirus vaccine multiplied by 1.28 to include herd immunity.

also obtained from local literature and experts' consultation with clinicians practicing in Korea.

Despite such efforts, some of the variables and assumptions challenge the validity of our results through the over- or under-

estimation of the cost-effectiveness of rotavirus vaccination. For example, the incidence of RVGE in 2006 may have been underestimated; this provides information on the size of the benefited population if RVs were provided by the NIP. We estimated the

Table 5
Cost-effectiveness of RV1 and RV5 in the scenario analyses.

Scenario number	Variable			ICER (USD/DALY averted)	
	Healthcare costs	Effective-ness	Vaccine price	RV1	RV5
1	High	High	Low	Cost-saving	12,617
2	Base-case	High	Low	Cost-saving	20,879
3	High	High	High	10,545	31,578
4	Base-case	High	High	18,800	39,840
5	Base-case	Low	High	30,803	52,100
6	Low	Low	High	58,169	79,462

DALY = Disability-adjusted life years. ICER = incremental cost-effectiveness ratio. RV1 = attenuated human strain originated monovalent vaccine (Rotarix®). RV5 = pentavalent human-bovine reassortant vaccine (Rotateq®). RVGE = rotavirus gastroenteritis. USD = US dollars.

All costs are estimated from the societal perspective and presented in 2018 US dollars. An exchange rate of 1 USD to 1100 Korean won is applied.

incidence of RVGE based on the RVGE diagnosis code (i.e., A08.0) from NHI claims records. Although this is a conventional approach that is commonly adopted by studies using insurance claims data, it has problems associated with under-identification, especially in non-severe RVGE cases, which are defined as those with outpatient visits only. In real practice, unlike severe RVGE cases that require hospitalization, outpatient visits for RVGE are less likely to be recorded with the RVGE diagnosis code in claims records. As the treatment for non-severe RVGE is not particularly different from that for common diarrhea or enteritis, clinicians do not have a strong motivation for recording RVGE as the diagnosis. In addition, although clinicians in outpatient settings may consider a case to be RVGE, they often skip the cumbersome diagnosis process, which includes fecal examination. These practice patterns may lead to under-recording of RVGE in insurance claims records and may have consequently resulted in the conservative ICER value obtained in the present study. To overcome such limitations, we performed additional sensitivity analyses, assuming that the incidence of severe RVGE requiring hospitalization is one-fourth of the incidence rate of non-severe RVGE [33,34]. Thus, we applied the incidence of non-severe RVGE as being four times as that of severe RVGE, defined as hospitalized cases with a diagnosis of RVGE in NHI claims records. This led to increases in the incidence rate of non-severe RVGE, resulting in lower ICERs (3929 USD per DALY averted for RV1, 14,373 USD per DALY averted for RV5, and 9412 USD per DALY averted for the application of both RV1 and RV5).

The data used for the estimation of the effectiveness of the RV in this model were obtained through the meta-analysis of post-licensure observational studies [20]. Each of those studies measured the effectiveness of the vaccine through its preventive effects with respect to hospitalization and emergency room visits due to RVGE (i.e., severe RVGE). However, we used the effectiveness measures to examine the prevention effect for non-severe RVGE as well, which may result in the overestimation of the vaccine's preventive capacity and have a positive effect on the cost-effectiveness of the vaccine.

The base-case model did not incorporate the vaccine's herd immunity effect, which refers to the indirect protection from RVGE conferred upon unvaccinated people when a large proportion of a population acquires RVGE immunity [35]. Therefore, our base-case analysis results, which only include the vaccine's direct preventive effect, may underestimate the vaccine effectiveness as well as cost-effectiveness. According to the further analysis reflecting herd immunity resulting from vaccination, RV1 was analyzed as a cost-saving alternative, and RV5 was also evaluated as a very cost-effective alternative, of which was smaller than 1 GDP per capita.

Since the quality of life measured for the same condition often varies across different populations or countries, using the value specific to the country in question is advisable. We used disability weights of mild and moderate diarrhea as measures of disutility

that patients experience with non-severe and severe RVGE, respectively [18]. Previous studies employing the UNIVAC (or TRIVAC) model for the economic assessment of RVs used disability weights of moderate and severe diarrhea as measures of disutility for non-severe and severe RVGE [15,36]. However, upon an advisory meeting with domestic experts, it was decided that non-severe RVGE should be defined as mild diarrhea and severe RVGE as moderate diarrhea in our evaluation of quality of life, generating results which are inconsistent with the GBD study value [27].

The annual inflation rate is one of the variables affecting future vaccine costs and healthcare costs related to RVGE. As the future inflation rate was considered to add uncertainty and since we confirmed that vaccine costs in Korea had not increased in the last 5 years, the annual inflation rate was not included in this analysis. Nevertheless, the healthcare costs for RVGE treatment are expected to undergo inflation in the future. Therefore, it is possible that the healthcare costs, without adjustment for the inflation rate, were underestimated; this could overestimate the ICER in the current analysis.

The present study compared a hypothetical scenario in which RVs were introduced into the NIP in 2018 with a hypothetical scenario in which no RVs were available in 2018. To estimate the occurrence of RVGE under the scenario involving unavailability of RVs in South Korea, we used the incidence data of RVGE in 2006, which were the most recent data before RVs became available in South Korea in 2007. However, it may not be realistic to assume that the incidence and epidemiologic characteristics of RVGE remained constant from 2006 to 2018. Considering that RVGE continues to occur around the world regardless of the level of income, we assumed that the incidence of RVGE might not have declined substantially from 2006 to 2018 if RVs were unavailable in South Korea. Nonetheless, we believe that the use of 2006 data may lead to over-estimation of the effectiveness of RVGE vaccination in our society, and, thus, our results should be interpreted with caution. According to 2016 data, the combined vaccination rate of the two RVs was 84.5%, and the prevalence of RVGE had significantly reduced following the vaccination [14]. Thus, the results of our analysis should be interpreted with an understanding that they are based on 2006 data, before the vaccine came into use, and that they do not reflect the current status.

As a result, this cost-effectiveness analysis suggests that introducing two RVs (RV1 and RV5) into the NIP in South Korea is a cost-effective alternative from a societal perspective and the ICER was robust within $2 \times$ GDP even when the variables were fluctuating. These results serve to help policymakers decide to include rotavirus vaccination into the NIP with evidence-based decision-making.

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Declaration of Competing Interest

None.

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