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Economic burden of rotavirus diarrhea in Thailand: Report from a pilot study on rotavirus vaccination

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ABSTRACT

Background: Rotavirus diarrhea is the leading cause of morbidity and mortality in young children in both developed and developing countries. Hospitalization costs are a significant burden of both governments and households. The objective of this study was to estimate the economic burden associated with the hospitalization of children with non-rotavirus and rotavirus diarrhea in two provinces in Thailand.
Method: A prospective incidence-based cost-of-illness study was conducted on children under five years old with acute diarrhea who had been admitted to public hospitals in two provinces during October 2012 and June 2013. Caregivers were interviewed to estimate costs from a societal perspective at 2014 values. Stool samples were examined for rotavirus antigens. Multivariate regression analysis was used to assess the relationship of predictor variables to costs. Annual economic burden of rotavirus hospitalization was estimated by multiplying the number of hospitalized children and the hospitalization cost per episode. The costs were converted to international dollars (I$) using purchasing power parity (PPP) (1 USD = 12.36 baht for the year 2014).
Results: Seven hundred and eighty-eight cases of acute diarrhea were included in the analysis. Of the total, one hundred and ninety-seven (25%) were detected as being rotavirus positive. Total societal costs of inpatient care per episode were 822.68 USD (10,165 Baht). The average costs of children with and without rotavirus were 903.39 USD (11,162 Baht) and 795.40 USD (9,827 Baht), respectively. Based on the multiple regression analysis, rotavirus infection, severity, and younger age were significantly associated with the higher costs.
Conclusion: Diarrhea, rotavirus diarrhea in particular, represents of a substantial economic burden in the society in Thailand. The accurate estimates that societal costs of the rotavirus diarrhea hospitalizations provide valuable input for considering a preventive program.

1. Introduction

Rotavirus is the predominant etiologic agent of severe diarrhea in children under five years of the age worldwide, especially in the low-and the middle-income countries in Sub-Saharan Africa and Southeast Asia [1–3]. It was estimated that in 2013 rotavirus globally caused approximately 37% of all diarrhea-associated hospitalizations, and 215,000 deaths in this age group [3]. Thailand, which has been classified as a middle-income country, addressed the disease burden of rotavirus diarrhea that the rotavirus-associated mortality rate was low with an estimated rate of 2.2 per 100,000 children per year in 2008, but the morbidity-associated hospitalization has been a problem of the accounting for 20% to 50% of children admitted with diarrhea [4,5].

Currently, an oral rotavirus vaccination is recommended as the best way to protect against rotavirus diarrhea. Even though the cost of new vaccines is higher than that of traditional vaccines, when considering the economic burden of the disease and the cost-effectiveness, but the vaccination may potentially still be considered economically viable. According to a part of such an analysis is one important factor for making decision process before

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implementing a program that concerns the exploring impacts of the intervention in the limited health budget. It is necessary to consider the economic burden of the disease. The treatment costs and the patients' costs of rotavirus diarrhea were limited in Thailand. Therefore, this prospective study aimed to determine the hospitalization cost of children with rotavirus and non-rotavirus diarrhea in two provinces in Thailand and to extrapolate to the Thai nationwide level. These findings were essential for the policy makers using the consideration of the introduction of rotavirus vaccination into the national immunization program.

2. Methods

2.1. Study site and population

This study was a prospective, incidence-based cost of illness analysis. The costs of hospitalization due to diarrhea were estimated from a societal perspective. As a part of a hospital surveillance [6], our study was conducted in twelve public hospitals (three general hospitals and nine district hospitals) in Phetchabun and Sukhothai provinces. History of rotavirus vaccination in both provinces was not explicitly taken into account. During the period from October 2012 to June 2013, we recruited children under 5 years old who had been admitted with diarrhea. The inclusion criteria were as follows: (i) Thai children aged 2–59 months, (ii) lived in the study areas, (iii) were admitted with diarrhea, which defined as experiencing three or more loose stools or one watery stool in a 24-hour period, (iv) their caregivers could communicate in Thai, and (v) their caregivers signed a consent form to participate in the research. Children who had underlying diseases, for example, bowel disease, immune deficiency or cardiovascular disease, were excluded.

According to the formula laid out in the World Health Organization (WHO) guidelines [7], using an estimate of 4,500 children with diarrhea from the two sites in the past year with a margin of error of 15% and the coefficient of variation of 1.69, the minimum sample size of all diarrhea cases was estimated at 440 patients. This coefficient of variation based on the results of preliminary data collected in the study with an average household cost of 378.99 USD (4,682 Baht) and the standard deviation of 638.82 USD (7,893 Baht). Therefore this study was a part of the hospital surveillance, all participants who met the eligibility criteria during the data collection period were included.

2.2. Data collection

The ward nurses, who had been trained on data collection, screened the hospitalized children following the eligibility criteria and explained all the details of this study to the caregivers. If the caregivers accepted, they signed the informed consent forms. The data were collected through the structured questionnaires and the medical records. Face-to-face interviews were used to collect data before and during hospitalization, while telephone interviews were conducted on the 7th day after discharge. All of the feces samples collected from the recruited children were examined for rotavirus antigens by the laboratory of the National Institute of Health Department of Medical Science, Ministry of Public Health, using polyacrylamide gel electrophoresis (PAGE). The study was approved by the Ethical Review Board of the Committee for Research in Human Subjects, Ministry of Public Health, Thailand (Ref. no. 10/2555).

Information on patients' characteristics, clinical data and cost data were collected. Their clinical severity was measured on the Vesikari scale [8,9], which includes 7 parameters: duration of diarrhea (days), maximal number of diarrheal stools per 24-hour period, duration of vomiting (days), maximal number of vomiting episodes per 24-hour period, maximal recorded fever (degree Celsius), dehydration, and type of treatment received. From a total of 20 points, scores $\geq$ 11 were classified as severe, 7 to 10 were classified as moderate and $\leq$6 were classified as mild. The cost data included both direct medical costs and direct non-medical costs. The figure of time cost of caregiver was included as a part of the direct non-medical cost [10,11]. For indirect costs, a morbidity cost of patient was not included because the patients were not at working age and a mortality cost was not considered because there were no reported diarrhea-related deaths in this study. Treatment costs of public health facilities within the study sites were extracted from medical databases e.g. medication, medical materials, laboratory investigations, room and medical services. The interviews were conducted to examine out-of-pocket costs (e.g. treatment cost, transportation, meals, accommodation, extra nappies, and food supplementations) and time loss of caregiver. The family expenditure was defined as all out-of-pocket expenses during children's illness by the family which consisted of both direct medical costs and direct non-medical costs.

2.3. Cost valuation

For unit costs of medication and medical materials were referred to the median reference price of Drug and Medical Supply Information, Ministry of Public Health, Thailand [12] and unit costs of laboratories, rooms and medical services were obtained from the standard cost lists for health technology assessment [13]. Appropriate corrections using the deflator were performed where needed, with conversion to 2014 values using the consumer price index [14]. The total costs of each category were calculated from the quantities of resources used multiplied by the unit costs. Treatment costs at private health facilities were based on charges because the cost-to-charge ratio of these settings has not been reported in Thailand. Caregivers' time costs equaled the number of days care for their children multiplied by their gross national income per day [15]. The cost of rotavirus testing was not included because it was for the research purposes only and not reflecting routine clinical practice.

2.4. Extrapolation of annual hospitalized cost due to rotavirus diarrhea

Annual national hospitalization costs were calculated from the average costs per rotavirus diarrhea resulting in hospitalization and the annual number of rotavirus hospitalizations, which were obtained from the Bureau of Epidemiology, Ministry of Public Health, Thailand and previous publication [16,17].

2.5. Data analysis

Data were double entered using Microsoft Excel and statistical analysis was performed using STATA 14.0 software. All costs were expressed in mean, median and 95% confidence interval (CI). The chi-square test or Fisher's exact test was used to analyze the qualitative variables. Comparisons between two groups of continuous variables was estimated using a Mann-Whitney *U* test. To assess the influence of predictor variables on costs, multivariate regression analysis (using enter method and stepwise method) of log-transformed costs was conducted. We have checked the model assumptions by examining the normality, heteroscedasticity and multicollinearity. When the models were under these assumptions, the costs were retransformed to the original scales adjusted by a smearing factor [18]. The statistical significance was set at a p-value < 0.05. Costs in Thai Baht were converted to the international dollar (I$) using purchasing power parity (PPP) (1 USD = 12.36 Baht in 2014) [19].

3. Results

A total of 788 children were included in the study. The patients' characteristics were as presented in Table 1. Of the total, 197 (25%) samples had positive test for rotavirus. The patients' mean age was 20.21 months. The mean age of children with rotavirus-associated hospitalization was higher in Sukhothai, where vaccination has taken place, than in Phetchabun (29.25 vs 24.42 months, $p < 0.008$). Comparison between children with rotavirus group and non-rotavirus group show that there was no significant difference in baseline characteristics except age and proportion of infection between two provinces.

As shown in Table 2, the lengths of stay in hospital of children experiencing rotavirus and non-rotavirus diarrhea were similar, in the range of 3–5 days. Children with rotavirus diarrhea had higher Vesikari scores than those with non-rotavirus diarrhea ($p < 0.001$) with approximately 80% being classified as severe. However this increase in severity was only caused by the figures for the maximum number of vomiting and duration of vomiting per day in the rotavirus group over the non-rotavirus group ($p < 0.001$).

Table 3 presents the cost per diarrhea episode. Care was sought for about 61% (470/776) of the hospitalized children before admission to hospital, with the average medical cost of the outpatient care prior to hospitalization being 19.97 USD (247 Baht). During admission, the average medical cost for all children was 521.22 USD (6,440 Baht) and that for children with rotavirus diarrhea was 573.86 USD (7,090 Baht), with the largest share of cost being on hospital bed-day and routine service. After discharge, 9% (70/787) of all patients were treated, with the average medical costs being 11.60 USD (143 Baht). The out-of-pocket treatment cost accounted for 11% of the total direct medical costs. For direct non-medical costs, the average costs of transportation, meals and other child care were 102.94 USD (1,272 Baht) and the cost of informal care was estimated to be 168.10 USD (2,077 Baht). In a comparison between rotavirus and non-rotavirus infections, neither the direct medical costs nor the direct non-medical costs were significantly different. The average total cost for rotavirus diarrhea was 903.39 USD (11,162 Baht), whereas that for non-rotavirus diarrhea was 795.40 USD (9,828 Baht).

The annual number of rotavirus-related to hospitalization in Thailand could be based on a total of 4.9 million cases of diarrhea in children aged under 5 years old as derived from reported cases of diarrhea per 100,000 population in this age group [16], and the risk of rotavirus requiring hospitalization at 1 in 85 [17]. This resulted in 58,035 cases of rotavirus requiring hospitalization and annual direct medical cost and societal cost at 36 million USD (395 million Baht) and 52 million USD (648 million Baht), respectively. The estimate of annual family expenditure was 22 million USD (266 million Baht).

To investigate the predictor variables affecting the costs, multivariate regression analysis was employed including potential predictor variables as shown in Table 4. All covariates had relatively small correlation (0.4–27%). Based on the fitted model (Table 5), the three significant variables which affected the costs were severity, presence of rotavirus infection and the child's age. It was found that rotavirus infection and severity had significant impacts on increasing the costs, whereas a younger child resulted in higher costs. To estimate the costs of rotavirus diarrhea of each age group by fitting the stepwise regression equations, which considered significant covariates, power of explanation and criteria information. The calculation of predicted costs of severe rotavirus diarrhea according to the ages were illustrated in Fig. 1. Increasing age represented the declining cost of illness.

4. Discussion

This study presents the first cost analysis of diarrhea in Thailand that was based on primary data collection of both patients and caregivers. Our findings provide evidence on substantial economic impact of hospitalization due to diarrhea from the societal perspective, in particular those related to rotavirus diarrhea. The length of stay during admission from 3 to 5 days was similar compared to previous studies [20–22]. Most cases were severe and children with rotavirus diarrhea had more vomiting than children

Table 1
Characteristics of hospitalized children classified by rotavirus detection.

Characteristic	All (n = 788)	Rotavirus (n = 197)	Non-rotavirus (n = 591)	p-value[a]
Age (months)				
Mean (SD, Median)	20.21 (13.68, 15.62)	26.63 (13.52, 25.83)	18.08 (13.06, 13.53)	<0.001[b]
Age group (months); n (%)				
≤24	548 (69.54)	95 (48.22)	453 (76.65)	<0.001[c]
25–48	201 (25.51)	89 (45.18)	112 (18.95)	
49–59	39 (4.95)	13 (6.60)	26 (4.40)	
Gender; n (%)				
Male	460 (58.38)	111 (56.35)	349 (59.05)	0.504[d]
Female	328 (41.62)	86 (43.65)	242 (40.95)	
Insurance scheme; n (%)				
UC	741 (94.03)	192 (97.46)	549 (92.90)	0.086[c]
CSMBS	38 (4.82)	5 (2.54)	33 (5.58)	
Self-payment	8 (1.02)	0 (0.00)	8 (1.35)	
Local government	1 (0.13)	0 (0.00)	1 (0.17)	
Province; n (%)				
Phetchabun	441 (55.96)	107 (54.31)	240 (40.61)	0.001[d]
Sukhothai	347 (44.04)	90 (45.69)	351 (59.39)	
Type of hospital; n (%)				
District	394 (50.00)	96 (48.73)	298 (50.42)	0.681[d]
General	394 (50.00)	101 (51.27)	293 (49.58)	

UC = universal coverage scheme, CSMBS = the Civil Servant Medical Benefit Scheme.
[a] To compare between rotavirus and non-rotavirus.
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.
[d] Chi-square test.

Table 2
Clinical features of hospitalized children.

Clinical characteristic	All (n = 788)	Rotavirus (n = 197)	Non-rotavirus (n = 591)	p-value[a]
Length of stay (days)				
Mean (SD, Median)	3.95 (1.58, 4)	4.13 (1.95, 4)	3.89 (1.44, 4)	0.502[b]
Vesikari score				
Mean (SD, Median)	13.04 (2.83, 13)	14.22 (2.41, 14)	12.65 (2.84, 13)	<0.001[b]
Level of severity; n (%)				
Mild	1 (0.13)	0 (0.00)	1 (0.17)	<0.001[c]
Moderate	155 (19.67)	11 (5.58)	144 (23.71)	
Severe	632 (80.20)	186 (94.42)	446 (76.12)	
Maximum number of stools per day; n (%)				
1–4	115 (14.59)	21 (10.66)	94 (15.90)	0.081[d]
5	198 (25.13)	45 (22.84)	153 (25.89)	
≥6	475 (60.28)	131 (66.50)	344 (58.21)	
Duration of diarrhea (days); n (%)				
1–4	441 (55.97)	107 (54.31)	334 (56.51)	0.853[d]
5	122 (15.48)	31 (15.74)	91 (15.40)	
≥6	225 (28.55)	59 (29.95)	166 (28.09)	
Vomiting; n (%)	600 (76.14)	180 (91.37)	420 (71.07)	<0.001[d]
Maximum number of vomiting episodes per day; n (%)				
1	61 (7.74)	12 (6.09)	49 (8.29)	<0.001[c]
2–4	263 (33.38)	58 (29.44)	205 (34.69)	
≥5	276 (35.03)	110 (55.84)	166 (28.09)	
Duration of vomiting (days); n (%)				
1	161 (20.43)	40 (20.30)	121 (20.47)	<0.001[d]
2	179 (22.72)	48 (24.37)	131 (22.17)	
≥3	260 (32.99)	92 (46.70)	168 (28.43)	
Fever; n (%)	750 (95.18)	190 (96.45)	560 (94.75)	0.745[d]
Dehydration; n (%)				
None	287 (36.42)	226 (38.24)	61 (30.96)	0.070[c]
1–5%	496 (62.94)	360 (60.91)	136 (69.04)	
≥6%	5 (0.64)	5 (0.85)	0 (0.00)	

[a] To compare between rotavirus and non-rotavirus.
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.
[d] Chi-square test.

Table 3
Cost of hospitalized patients per episode (USD in 2014) classified by rotavirus detection.[*]

Type of cost	All (n = 788)		Rotavirus (n = 197)		Non-rotavirus (n = 591)		p-value[a]
	n	Mean, Median (95%CI)	n	Mean, Median (95%CI)	n	Mean, Median (95%CI)	
Direct medical cost	776	551.38, 475.49 (528.52, 574.25)	196	612.37, 792.93 (550.84, 673.90)	580	530.77, 472.26 (508.54, 553.01)	0.336
Before hospitalization[b]	776	19.97, 8.93 (16.54, 23.40)	196	26.34, 9.94 (16.50, 36.17)	580	17.83, 8.34 (14.67, 20.98)	0.087
Hospitalization	788	521.22, 457.60 (498.85, 543.59)	197	573.86, 474.04 (512.15, 635.57)	591	503.67, 453.59 (482.22, 525.12)	0.662
Medication		32.46, 23.85 (29.82, 35.09)		38.22, 25.05 (29.80, 46.64)		30.54, 23.52 (28.44, 32.63)	0.810
Medical material		29.25, 5.71 (24.84, 33.67)		32.41, 5.13 (21.69, 43.41)		28.20, 5.87 (23.52, 32.88)	0.573
Laboratory		40.24, 31.43 (36.87, 43.61)		44.15, 30.69 (36.41, 51.90)		38.94, 31.83 (35.26, 42.61)	0.653
Room and routine service		419.27, 395.61 (402.03, 436.51)		459.08, 397.25 (412.62, 505.53)		406.00, 395.61 (389.12, 422.88)	0.380
After hospitalization[c]	787	11.60, 0 (5.64, 17.55)	197	23.31, 0 (4.65, 41.96)	590	7.68, 0 (2.78, 12.59)	0.737
Direct non-medical cost							
Travel, food, extra diapers and others	773	102.94, 81.60 (97.09, 108.80)	195	113.91, 84.88 (99.01, 128.82)	578	99.24, 78.91 (93.26, 105.22)	0.126
Informal care	788	168.10, 148.43 (160.66, 175.54)	197	173.72, 148.43 (155.44, 191.00)	591	166.39, 148.43 (158.43, 174.35)	0.943
Total cost	768	822.68, 720.98 (791.92, 853.43)	194	903.39, 747.41 (820.46, 986.31)	574	795.40, 717.92 (765.54, 825.25)	0.273

[*] All costs were in international dollars for the year 2014.
[a] To compare between rotavirus and non-rotavirus using Mann-Whitney *U* test.
[b] Mean costs were calculated from the costs of 470 patients (127 patients in rotavirus group and 343 patients in non-rotavirus group) who were treated before hospitalization divided by total number of cases who completed follow-up.
[c] Mean costs were calculated from the costs of 70 patients (16 patients in rotavirus group and 54 patients in non-rotavirus group) who were treated after hospitalization divided by total number of cases who completed follow-up.

with non-rotavirus diarrhea [23–25]. Generally, a diagnostic test for rotavirus antigens is not clinical routine practice. Treatment is primarily based on clinical status, therefore the management of rotavirus or other infectious pathogens is not particularly different [23]. However, it should be noted that rotavirus testing was performed in our study. Our unadjusted results were consistent with those of other similar studies [26–28] in that there was no significant difference in terms of costs between children with and without rotavirus diarrhea. However, in this study, after adjusting for the confounders, the cost of treating children with

Table 4
Potential predictor variables included in the multiple regression analysis.

Variables	Definition	Code and values
Dependent variables		
LnDMC	Natural logarithm of direct medical cost	Number in LN form of direct medical cost
LnTotalcost	Natural logarithm of total cost of illness	Number in LN form of total cost
Independent variables		
Age	Child's age (months)	Mean of age = 20.21 months
Severity	Severity level	1 = severe (80.20%), 0 = mild to moderate (19.80%)
Gender	Child's gender	1 = female (41.62%), 0 = male (58.38%)
Insurance scheme	Universal Health Coverage (94.04%) as reference	
CSMBS	Civil Servants Medical Benefit scheme (4.82%)	1 = Civil Servants Medical Benefit scheme, 0 = else
Cash	Self-payment (1.02%)	1 = Self-payment, 0 = else
Others	Local government scheme (0.13%)	1 = Local government, 0 = else
PV	Province	1 = Phetchabun (44.04%), 0 = Sukhothai (55.96%)
LH	Level of hospital	1 = District hospital (50%), 0 = General hospital (50%)
RV	Rotavirus infection	1 = Yes (75%), 0 = No (25%)

Table 5
Multiple regression analysis of the cost per diarrhea episode.

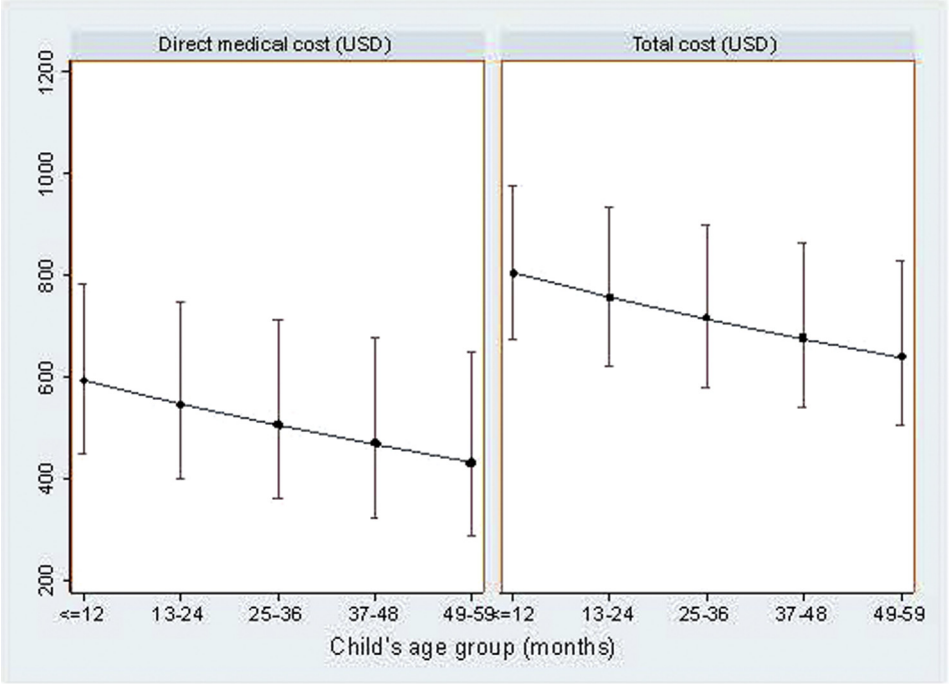
Variables	Direct medical cost						Total cost of illness					
	Enter			Stepwise			Enter			Stepwise		
	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
Constant	438.31	23.80	<0.001	443.50	20.20	<0.001	682.51	33.21	<0.001	688.09	28.03	<0.001
Child's age (months)	0.993	0.001	<0.001	0.993	0.001	<0.001	0.993	0.001	<0.001	0.993	0.001	<0.001
Female	0.992	0.036	0.819				0.966	0.031	0.286			
Insurance scheme												
CSMBS	0.936	0.078	0.430				0.943	0.070	0.428			
Cash	1.008	0.177	0.965				1.043	0.163	0.789			
Others	1.439	0.711	0.462				1.457	0.640	0.392			
Phetchabun Province	1.041	0.038	0.277				1.050	0.034	0.134			
District Hospital	0.996	0.036	0.919				1.000	0.033	0.996			
Severe score	1.278	0.058	<0.001	1.275	0.058	<0.001	1.261	0.051	<0.001	1.259	0.051	<0.001
Rotavirus infection	1.083	0.047	0.066	1.092	0.047	0.040	1.082	0.042	0.044	1.091	0.042	0.024
Adjusted R^2	0.058			0.062			0.073			0.074		
AIC[a]	1,110.03			1,100.56			917.91			910.91		
BIC[b]	1,156.57			1,119.17			964.34			929.49		

[a] AIC Akaike Information Criterion.
[b] BIC Bayesian Information Criterion.

rotavirus infection was significantly higher than those without rotavirus infection. The higher costs of rotavirus group may be caused from more frequency and duration of vomiting which increased a greater severity of dehydration. This was associated with a longer length of stay and incurred a higher cost for taking care of child. The hospitalization cost of rotavirus diarrhea could be underestimated to be lower than expected because some children in Sukhothai received rotavirus vaccination which reduced the rotavirus severity [6].

In regression models, the independent variables for costs had small power (Adjusted R^2 = 0.058–0.074) in explaining costs, the significant factors identified for this association were consistent with previous studies [29–32]. However the variables would additionally investigate in future modeling. The treatment costs were not different between the study sites in both bivariate analysis and multivariate regression analysis. The hospitalization cost was a major economic burden of rotavirus diarrhea by range 40% to 80% of the overall costs [33–36]. The main cost driver of direct medical costs was the hospital bed-day cost (reflecting 55% of the overall costs) which was consistent with previous studies [22,28,37,38]. The average out-of-pocket payment of hospitalization associated with rotavirus diarrhea was 370.38 USD (4,577 Baht), corresponding to 40% of total cost of illness.

Previous studies examining the cost of rotavirus in middle-income countries were identified. To be able to compare, all costs were converted to 2014 levels using the inflation rate of each country and then adjusting for purchasing power parity (PPP) reported below [19,39]. Due to lack of primary data related to inpatient cost-associated rotavirus diarrhea in Thailand, Chotivitayatarakorn et al. (2010) used the direct medical cost of hospitalized patients (including costs of personnel, capital, food and bed-day except medications and diagnostic tests) of 99.55 USD estimated from WHO-CHOICE [40]. While another study in Thailand (2012) adopted inpatient cost of 252.58 USD from cost of bacterial diarrhea (recruiting both children and adults and including cost of medicine, medical material and laboratory) [41]. In Malaysia, Lee et al. (2002) reported median direct medical cost of rotavirus hospitalization from 393 children aged less than 14 years at a teaching hospital in the urban area. The median cost of 520.96 USD were estimated from treatments, laboratory tests, salaries of staffs and bed-days [42]. In Vietnam, Fischer et al. (2003) obtained cost data from 90 children aged below 5 years by combining direct medical costs (medications, diagnostic tests and hospital bed-days), direct non-medical costs (transportation) and indirect costs (time lost while taking caring of the sick children). The societal cost of inpatient care ranged between 60.55 USD and 70.63 USD [43]. In Indonesia (2007), 891 children less than five years of age were recruited from public and private hospitals [44]. The study covered direct medical costs (medications, diagnostics and bed costs), direct non-medical costs (transportation) and indirect costs (time



Cost by age group (USD)	<=12	13-24	25-36	37-48	49-59
Direct medical cost	593.72	547.02	505.67	467.44	432.11
Total cost	908.15	835.36	771.02	711.63	656.81

*Upper and Lower bound of costs were calculated from 95% confidence interval of each coefficient

Fig. 1. Expected costs of severe rotavirus diarrhea for child's age group (USD in 2014).

loss of caring the sick children) and the average direct medical cost and total cost of hospitalization were 79.75 USD and 107.69 USD, respectively. Another study in Kenya recruited 172 admitted children under the 36 months of age in the national referral hospital [38]. Direct costs included treatments costs prior and during hospitalization, and indirect costs concerned travel and caregivers' time cost during children's illness. It was found that the hospital cost and the societal cost per rotavirus episode was 107.29 USD and 183.40 USD, respectively. Even though Kenya has a lower per capita GNI as Vietnam and Indonesia, the cost per episode was higher, which was different at level of healthcare facilities. The referral hospital may see more severe cases or co-morbidities and have more expensive in some cases used specialized equipment or personal that stayed more. We do note, however, that a direct comparisons between these studies should be made with caution as study design, healthcare facilities, the scope of health utilization, and socio-economic status may have been different.

The annual cost incurred of children hospitalized due to rotavirus diarrhea was substantial. Rotavirus caused ~58,000 hospitalizations per year in children under the five years of age, resulting in 52 million USD for total annual societal cost (or 8% of the gross national income per capita each diarrheal episode). The total costs of rotavirus diarrhea would increase in case of including episodes of outpatient visit and self-medication. It is likely that the introduction of a rotavirus vaccine, providing good protection against severe diarrhea, into the national immunization program in the future, would reduce the number of rotavirus-related hospital admissions and the cost burden by 88% [6].

PAGE is a standard method for the detection of rotavirus infection [45]. In this study, PAGE was used due to practicability in our laboratory and its low cost. Using PAGE may lead to higher false negative result when compared with other molecular method such as the reverse-transcription polymerase chain reaction (RT-PCR) [46,47]. However, if RT-PCR was used, it would result with the higher false positive rate [45,48].

One important strength of our study is that the data collected relate directly to Thailand, covering both rural and urban areas and a wide variety of public hospitals. A second strength concerns the broad variety of types of collected costs and the use of consistent cost collection methods within the different settings. A third strength, no selection bias of the non-Thai speaking community occurred in our study. We excluded two children of Myanmar migrant workers so there was no non-Thai speaking community in our study area. Obviously, some limitations applied as well. Firstly, the economic burden was based on cost data reported by district hospitals and general hospitals and we could not reach the details of treatments from teaching hospitals and private hospitals, hence generalization to the national level should be considered with appropriate care. Secondly, the present study did not include the cost of diarrhea-associated outpatient visits or home treatments, thus the total cost still represents an underestimation of the true burden of the disease. Thirdly, we did not identify non-rotavirus pathogens related to acute diarrhea in pediatric patients and not consider the seasonal pattern of enteric infection all the year round. If a new strain of other enteric pathogens (e.g. norovirus) emerged, it may lead to more severe of non-rotavirus cases. The hospitalization cost of non-rotavirus diarrhea could be higher than expected. This may have confounded in non-rotavirus samples and explain the marginal difference between rotavirus and non-rotavirus group. Fourthly, mortality is a driver of the burden in terms of life-years lost. There were no diarrhea-related deaths during the study period because of probably short-term

surveillance and limited sample sizes thus it was not possible to generalize to national level. Further study needs the very large sample sizes and more time to explore the mortality estimates in these ages. Fifthly, no history of rotavirus vaccination was obtained. Future studies involving the stool sampling during diarrhea episodes may additionally correct this issue. Lastly, our study chose non-rotavirus diarrhea as comparison group beyond our specific objectives on the cost-effectiveness analysis of rotavirus vaccination. Hence no comparison between non-diarrhea cases and rotavirus diarrhea cases did not reflect the potential opportunity costs for other diseases.

5. Conclusion

The hospitalization cost of diarrhea has resulted in substantial economic burden for society. The cost of treating children with rotavirus infection was higher than that of treating those without the rotavirus infection. These data would help the decision makers in the awareness of burden of rotavirus disease and the consideration of the preventive program for this disease.

Author contributions

OR, AR, PT, and SJ conceptualized and designed the study. OR, PT and SJ collected data. OR and AR analyzed the data and drafted the manuscript. MT and MJP contributed to the study design and to the discussion. All authors revised and approved the final manuscript before submission.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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