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Lee et al. Cost-effectiveness of Rotarix in the Philippines

ORIGINAL ARTICLE

COST-EFFECTIVENESS ANALYSIS OF UNIVERSAL MASS VACCINATION WITH *ROTARIX*® IN THE PHILIPPINES

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ABSTRACT

Background: Rotavirus is among the leading causes of severe gastroenteritis in children. Effective vaccines enable universal mass vaccination (UMV) which incurs high expenditure and therefore economic justification is needed.

Objective: This study aimed to evaluate the cost-effectiveness of UMV with *Rotarix*® versus no vaccination program in the Philippines.

Methods: A four-state decision tree model was used to estimate costs and health outcomes subject to annual discount rate of 3.5%. Local and international published data and experts' opinions were used for epidemiology, efficacy and resource use input parameters. Analyses were reported as estimated total costs, quality adjusted life years (QALYs) gained, and incremental cost-effectiveness ratio (ICER) in Philippines Peso (PHP) per QALY gained between rotavirus UMV and no vaccination.

Results: From a payer (societal) perspective, the ICER is PHP 12,835/QALY (PHP 12,059/QALY). Sensitivity analyses showed the ICERs below PHP 80,000/QALY, well below 1 time 2012 GDP per capita at PHP 103,366, with the main drivers of uncertainty being the probabilities of mild and moderate diarrhoea and vaccine costs.

Conclusion: Rotavirus UMV reduces both health and economic burden of rotavirus induced gastroenteritis. Based on the WHO's recommended thresholds, *Rotarix*® vaccination is projected to be very cost-effective in the Philippines in comparison with no vaccination.

KEYWORDS:
Rotavirus vaccine, Rotarix

INTRODUCTION

Rotavirus (RV) remains a leading cause of both morbidity and mortality among children in the Philippines. It is among the top ten causes of morbidity, and is the fifth leading cause of infant mortality with an estimated 5,000 deaths per year among children under the age of 2 years.[1] Rotavirus infection is particularly frequent in children younger than 5 years of age, with peak incidence in those aged less than 1 year.[2] The severity of the disease is reflected by the high number of hospital admissions for rotavirus-associated diarrhea. In a study conducted in seven centers in Muntinlupa City, Carlos *et al.* found that the prevalence of rotavirus was 31% among children hospitalized with diarrhea, and 30% among those who were presented to the emergency department. In the same region rotavirus results in approximately 84,590 clinic visits annually among children aged under 5 years.[3] In addition to the clinical symptoms of diarrhea, fever, vomiting, dehydration and possibly death in severe and untreated cases[4], there is significant impact on the quality of life for both the afflicted children and their caregivers. This also imposes considerable utilization of resources resulting in financial burden on health authorities. In developing countries where the prevalence of rotavirus gastroenteritis is high, there is potential for reducing morbidity and mortality using a childhood universal mass vaccination (UMV) program against rotavirus.[5]

The World Health Organization (WHO) recommends that rotavirus vaccines should be included for infants in national immunization programs, especially in developing countries where diarrheal deaths account for 10% or more of mortality among children aged 5 years and younger.[6] Strain typing studies in the Philippines have also shown that the disease burden can be attributed to strains against which current vaccines have proven to be effective, further highlighting the potential protection through rotavirus vaccination.[3] In several European countries such as Austria, Belgium, Finland and United Kingdom, rotavirus vaccines have been included in their routine vaccination programs.[7]

There are currently two vaccines available for use against rotavirus related disease: *Rotarix*® (GlaxoSmithKline, Brentford, United Kingdom) and *RotaTeq*® (Merck & Co., Whitehouse Station New Jersey, United States). *Rotarix*® is a human, live attenuated rotavirus vaccine containing a rotavirus strain of G1P [8] and *RotaTeq*® is a live naturally attenuated pentavalent bovine-human reassortant vaccine containing the four human G serotypes (G1-G4) and a human P serotype (P1A [8]). Both are orally administered with a schedule of two- and three-doses, respectively. Both available rotavirus vaccines have demonstrated efficacy against rotavirus gastroenteritis in clinical trials and effectiveness in real world settings.[8-9]

As the inclusion of a new vaccine in the national universal immunization scheme incurs considerable financial burden, an economic evaluation of UMV against rotavirus infection is vital to inform decision makers. Currently, rotavirus vaccination is only provided free of charge to the very poorest children in the Philippines. Therefore, the main objective of this study was to compare the costs and outcomes of a UMV program with *Rotarix*® versus no UMV program through a cost-effectiveness analysis in the context of the Philippines.

METHODS

A decision tree analytic model was developed to estimate the cost and outcomes of implementing a UMV program using *Rotarix*® compared to no vaccination program in the context of the Philippines. Similar evaluations have been published in the context of other countries such as Turkey.[10] We performed a cost-

effectiveness analysis with incremental cost per QALY gained from payer and societal perspectives separately.

In the base case analysis, vaccination coverage of 100% (i.e. all children in a hypothetical birth cohort received vaccination) and a full compliance with 2-dose regimen of *Rotarix*® were assumed.

Model structure and analytical approach

In the deterministic excel based decision tree model (see Figure 1), there are four health states based on the defined severity of diarrhea which is the key clinical manifestation of rotavirus induced gastroenteritis that may result in life-threatening dehydration.

- Mild – mild symptoms for which no medical advice is sought (for example, recovery at home) with an assumption that the case would last 2 days with 3 episodes of diarrhea per day (where diarrheal episodes are passages of loose stools)
- Moderate – symptoms for which some form of medical care is needed (for example, a visit to a general practitioner or equivalent medical professional depending on local practice) with an assumption that the case would last 5 days with 5 episodes of diarrhea per day
- Severe – when hospitalization is necessary with an assumption that the case would last 5 days with 8 episodes of diarrhea per day
- Rotavirus-related death

As the majority of rotavirus-related diarrhea cases and hospital admissions occur before the age of 5 years, children from birth up to 5 years are considered to be most vulnerable with peak of the risk in the first 24 months of life.[11] In the Philippines, Carlos *et al.* demonstrated that the peak of rotavirus infection is in the first 3-5 months of life.[3] Hence, the model is structured around the first 5 years of life with a hypothetical cohort of children being divided into 5 age-specific groups (i.e. 0-1 year, 1-2 years, 2-3 years, 3-4 years and 4-5 years). Each group was assessed at the same time over a model projection period of one year.

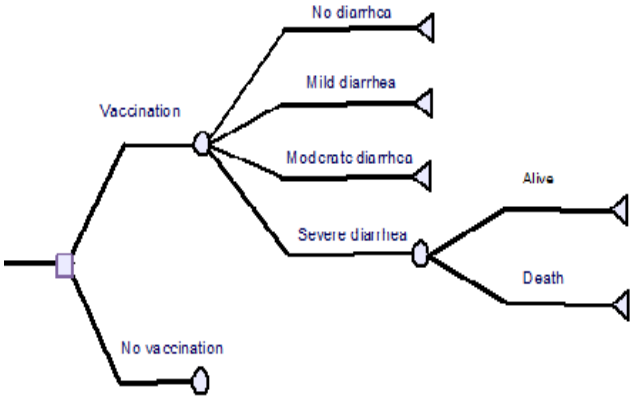

Figure 1. Decision tree for cost effectiveness analysis of universal mass vaccination versus no vaccination against rotavirus infection

A group of children below 1 year of age who have been vaccinated would have varying probabilities of facing the possible outcomes namely no diarrhea, mild, moderate and severe (see Figure 1). Only in the case of severe diarrhea, there would be a probability for the risk of death among those who have been hospitalized. For comparison against the scenario of no vaccination program, the same age group of children were assumed to face the same possible health outcomes but with different set of probabilities because of the absence of the vaccine protection effect. The same applies for each different age group of children as outlined above.

Data inputs

The model data inputs were taken from peer-reviewed sources through literature search. In the absence of published data, local pediatric experts in the management of diarrheal cases were consulted for their opinion (Dr Felizardo

Gatcheco, Manila Central University–Filemon D. Tanchoco Medical Foundation and Dr Jossie Rogacion, University of Philippines College of Medicine). The resource use and cost data were estimated based on expected costs of treatment using 2011-2012 estimates provided by the experts. In addition, the model structure was validated by the same experts to ensure that local clinical practice in managing children with gastroenteritis was reflected in the model.

Demographic data

The number of live births in the Philippines as recorded by the Field Health Service Information System in 2010 was 1,745,190 babies.[12] Assuming negligible infant and childhood mortality, there would be same number of children in age group 2-3 years in 2013. Under the same assumptions, by applying the average annual population growth rate of 1.9% for period 2000 to 2010 in the Philippines[13], the number of children for each age group was estimated as follows: 1,812,137 (0-1 years); 1,778,349 (1-2 years); 1,745,190 (2-3 years); 1,712,650 (3-4 years); and 1,680,716 (4-5 years).

Epidemiological data

In the absence of longitudinal real world local data recorded in a rotavirus specific disease registry, inputs from local experts and data reported in other Southeast Asian countries[3, 14-16] and the United States[17] were used and extrapolated to provide estimated incidence rates of rotavirus induced gastroenteritis in the Philippines. It was assumed that all babies experience some form of diarrhea, on average with 37.8% attributed to rotavirus. The estimated rotavirus incidences (per 100,000/year) were 37,800; 7,958; 796 and 202 for mild disease, moderate disease, severe disease and death, respectively.

Using these estimated incidence rates, probabilities of each age group of children falling into all the possible health states were estimated. These probabilities should be age-specific for the fact that immunity develops as a child grows older. In addition, the immunity against rotavirus infection also arises from any previous infection. Studies show that children are unlikely to die from rotavirus induced gastroenteritis after age 2 years.[18]

In the absence of published probabilities for the various health states in the Philippines, a number of assumptions were made and validated via expert opinion:

- Approximately 40% of the birth cohort will suffer mild rotavirus diarrhea over a period of 5 years for which no medical care is sought.
- For moderate cases where some form of medical help is needed, the probability of seeking such medical care is usually higher among younger children for whom the disease is likely to be more severe. This probability is assumed to decrease and remain stable after the first two years of life.
- Approximately 0.9% of the birth cohort will require hospitalization for severe rotavirus diarrhea in developing countries. While the disease is more likely to be severe in developing countries for many segments of the population thereby enhancing the risk of hospitalization, actual needed hospitalizations may not occur due to limited access (both physically and financially) i.e. the hospitalization rates may be lower than in developed countries regardless of actual disease severity.
- In developing countries, it is assumed that the overall probability of dying from rotavirus infection is less than 0.2, decreasing to 0 as children get older.

All probabilities are age-specific and higher in the lower age-groups (Table 1).

Vaccine effect

Probability for health states of vaccinated children were extrapolated from the data

available in Latin American countries with comparable socioeconomic status to the Philippines. Vaccine efficacy against severe rotavirus induced gastroenteritis and death were taken as 80.5% and 83%, respectively[19] with mild and moderate RVGE as 52% and 55%[20] respectively.

In order to take a conservative approach to the cost effectiveness analysis, only direct vaccine effects were considered, with the herd effect typically conferred by a UMV program not taken into account.

The probabilities of falling into the different possible health states for vaccinated children by age group are shown in Table 1. The probability of getting diarrhea among the vaccinated children is calculated as a function of the probability of getting diarrhea in the absence of vaccination, the vaccine efficacy for each of the respective health states, as well as the vaccination coverage assumed.

Resource use and cost data

This study was undertaken from two perspectives (payer and societal), with different cost elements considered. Only direct medical costs were included in the analyses based on payer perspective, and additional costs (e.g. direct non-medical costs, and indirect costs) were considered in separate analyses based on societal perspective. All costs were converted and reported in Table 2 in 2013 Philippine pesos (PHP).

The WHO treatment guidelines for diarrhea were used to estimate the resource use. Management of diarrhea consists of paracetamol for fever, oral rehydration salt sachets to prevent dehydration[21] and zinc supplementation.[22]

Direct medical costs were estimated by multiplying the local unit cost by the number of corresponding resource utilization unit for each costing element as listed in Table 2. The direct costs of these health states were assumed to remain regardless of age. A conservative approach was adopted and future costs were not considered as it is difficult to accurately quantify conditions requiring long-term medical care (such as growth stunting) that can be attributed to rotavirus induced gastroenteritis.

Vaccine costs considered for UMV were assumed to be PHP 866 per full course of vaccination i.e. 2 doses of *Rotarix®*. Rotavirus vaccination was also assumed to be administered as part of the existing primary vaccination schedule and hence is unlikely to incur significant additional administrative costs.

Direct non-medical costs included additional diapers used as the result of diarrhea and transportation to seek medical care. Loss in earnings as a result of parents staying home to care for children ill with diarrhea was estimated as part of the indirect costs. Productivity loss was calculated by taking into account the estimated number of days lost from work, the likely salary per day as well as the employment rate among the care takers. The average income per day for caregivers (PHP 1,000) and proportion of caregivers who worked (37.2%) reported in Bravo *et al.*[23] were used in the above mentioned estimation.

Table 1. Estimated probabilities of various health states for vaccinated and non-vaccinated children, by age group

Age group (Years)	No diarrhea		Mild		Moderate		Severe		Death	
	Vx[1]	Non-Vx[2]	Vx[1]	Non-Vx[2]	Vx[1]	Non-Vx[2]	Vx[1]	Non-Vx[2]	Vx[1]	Non-Vx[2]
0 – 1	0.89	0.37	0.087	0.18	0.0257	0.32	0.0014	0.13	0.0003	0.27
1 – 2	0.95	0.63	0.043	0.09	0.0080	0.20	0.0003	0.08	0.00005	0.24
2 – 3	0.97	0.80	0.028	0.06	0.0026	0.10	0.0000	0.04	0.000007	0.20
3 – 4	0.99	0.81	0.024	0.05	0.0022	0.10	0.0000	0.04	0.00	0.00
4 – 5	0.99	0.85	0.013	0.03	0.0012	0.10	0.0000	0.02	0.00	0.00

[1] Vaccinated; [2] Non-vaccinated

Table 2. Resource use and unit costs for each health state

Health state & costing items	Units	Cost/unit (PHP)	Sources
Mild			
• *Direct medical cost*			
Oral rehydration salts (ORS)	6 sachets	8	The Generics Pharmacy Price list[24]
Paracetamol drops	1	47	The Generics Pharmacy Price list[24]
• *Direct non-medical cost*			
Additional diapers	3 cases/day x 2 days	6	The Generics Pharmacy Price list[24]
Transportation	No medical care	0	Expert opinions
• *Indirect cost*			
Caregiver days at home	0 day		Expert opinions
Average income per day for caregiver		1,000	Bravo *et al.*[23]
Moderate			
• *Direct medical cost*			
GP visits (1st for the diarrhea episode & 2nd for follow-up)	2 visits	400	Expert opinions
Oral rehydration salts (ORS)	25 sachets	8	The Generics Pharmacy Price list[24]
Paracetamol drops	1	47	The Generics Pharmacy Price list[24]
Zinc Syrup	3	63	The Generics Pharmacy Price list[24]
Routine stool test	1	75	Expert opinions
• *Direct non-medical cost*			
Additional diapers	5 cases/day x 5 days	6	The Generics Pharmacy Price list[24]
Transportation	2 GP visits	32	Expert opinions
• *Indirect cost*			
Caregiver days at home	1 days		Expert opinions
Average income per day for caregiver		1,000	Bravo *et al.*[23]
Severe			
• *Direct medical cost*			
Hospitalization at a public hospital	1	8,100	Bravo *et al.*[23]
• *Direct non-medical cost*			
Additional diapers	8 cases/day x 5 days	6	The Generics Pharmacy Price list[24]
Transportation		207	Bravo *et al.*[23]
• *Indirect cost*			
Caregiver days at home	3 days		Bravo *et al.*[23]
Average income per day for caregiver		1,000	Bravo *et al.*[23]

In addition to improved health outcomes, a prevention of cases through vaccination would also result in potential cost savings over time as utilization of medical resources is reduced. However, vaccination does require a substantial amount of cost.

Disutility scores and QALY loss

Quality-adjusted life year (QALY) measures the effectiveness of a vaccine through a single index which is a combination of both the quantity and quality of life with the latter being measured through a health utility index. Disutility scores for each health state were taken from Postma *et al.*[20] Loss in quality-adjusted life years (QALY) was calculated for each health state as the product of the disutility weight related to the relevant event multiplied by the duration of exposure to the event expressed in the unit of year. Additionally, for simplicity, patients were assumed to be in full health i.e. the utility score = 1 after the gastroenteritis event with no recurrent episode. For example, the disutility score for mild state is -0.15 and each mild case was assumed to last 2 days. Thus, the QALY loss would be -0.00082 (-0.15*2/365). Similarly, the disutility score for moderate and severe health states are -0.25 and -0.7 respectively, resulting in QALY losses of -0.00342 and -0.00959.

In the event of death, for simplicity, we assumed that their QALY loss per death equal to the average life expectancy at birth in the Philippines which is 69 years.[25]

As vaccination would avoid a significant number of diarrhea episodes and also avert deaths, smaller QALY loss was expected than those estimated for the absence of vaccination. In the case of a death, the QALY loss would be measured over an average life-time such as the life expectancy in the Philippines (with an annual discount of 3.5%). Therefore, the more death averted through a universal mass vaccination program would in turn result in smaller QALY loss.

Cost-effectiveness analysis

Primary outcomes of interest were costs, QALYs gained, and the incremental cost-effectiveness ratio (ICER) in PHP per QALY gained. The ICER is defined as the difference in costs expressed with respect to the difference in effects (QALYs in this instance) between two interventions: *Rotarix*® vaccination vs. no vaccination. Usually, a new intervention is likely to improve health outcomes (for example, averted cases which would have occurred in the absence of the intervention) but at an additional cost.

All costs and outcomes were estimated for the cohort size of children up to the age of 5 years. Smaller QALY loss was expected from the benefits of cases of diarrhea and death averted through a UMV. Therefore, a QALY gain would result when a difference in QALY was calculated from a comparison against a greater QALY loss when no vaccination program was implemented. The QALY gained was discounted at a rate of 3.5% per year as recommended by the local National Center for Pharmaceutical Access and Management guidelines.[26] The results were presented as ICER for vaccination vs. no vaccination.

$$ICER = \frac{Cost_{vaccination} - Cost_{No\ vaccination}}{QALY_{vaccination} - QALY_{No\ vaccination}}$$

The interpretation of cost-effectiveness of our findings is based on WHO guidelines for developing countries.[27] The threshold value of cost-effectiveness is defined in relation to the Gross Domestic Product (GDP) of a country: highly cost-effective for an ICER <1 GDP per capita of the country; cost-effective for an ICER is between 1 to 3 times GDP per capita of the country; and not cost-effective for an ICER >3 times GDP per capita

of the country. The 2012 GDP in the Philippines per capita was PHP 110,314.[28]

Table 3. Variables and range of values for one-way sensitivity analyses

Variable	Health State	Base case	Min	Max
Total direct cost	Mild	95	76	114
	Moderate	1311	1049	1573
	Severe	8100	6480	9720
	Vaccine	866	693	1039
Duration (days off work)	Mild	0.000	0.000	2.000
	Moderate	1.000	0.800	1.200
	Severe	3.000	2.400	3.600
Probability	Mild	0.180	0.144	0.216
	Moderate	0.317	0.253	0.380
	Severe	0.126	0.101	0.152
	Death	0.270	0.216	0.324
Utilities	Mild	-0.002	-0.001	-0.002
	Moderate	-0.001	-0.001	-0.001
	Severe	-0.006	-0.005	-0.007
QALY loss for each death event	Death	-69	-55.2	-82.8
Vaccination coverage	Coverage	1.000	0.800	1.000
Discount	Discount rate	3.5%	2.8%	4.2%
Vaccine effect	Mild	0.52	0.796	0.921
	Moderate	0.55	0.840	0.963
	Severe	0.805	0.644	0.966
	Death	0.83	0.664	0.996
Average income per day (PHP)	Same for all states	1000	500	1500

Sensitivity analyses

One-way sensitivity analyses were performed to investigate the effects of altering parameters within plausible ranges of ±20% for each of the base-case value parameters and the 95% confidence interval for vaccine efficacy (Table 3). Two multivariate analyses were completed for the best scenario and the worst scenario by simultaneously taking all the minimum and maximum values together, respectively, for the parameters included in the one-way sensitivity analysis.

RESULTS

Estimated health and economic burden without universal vaccination program

A total of 719,871 mild diarrhea cases were estimated to occur across the age groups. For moderate and severe diarrhea, 158,331 and 16,353 cases were estimated, respectively. The annual total associated cost was estimated at PHP 543,344,218, with direct medical costs accounting for 75% of the total cost (Table 4).

Table 4. Estimated health and economic burden in the absence of a universal mass rotavirus vaccination program

	Estimated cases per year	Estimated costs per year (PHP)
Direct Medical costs		
Mild (719,871 cases)	719,871	68,387,779
Moderate (GP visit)	158,331	207,572,285
Severe (hospitalization)	16,353	132,459,360
Death	4,190	-
Subtotal	-	408,419,524
Direct non-medical costs	-	67,108,059
Indirect costs	-	67,816,635
Total	-	543,344,218

***Rotarix*® vaccination program vs. no vaccination**

Base Case

With a universal mass vaccination program in place for a cohort of nearly 2 million newborns in a year, the model predicted that 374,333 mild cases and 87,082 moderate cases of rotavirus related

diarrhea cases could be averted. At the vaccine efficacy of 80.5% and 83% against severe diarrhea and death, respectively, a UMV program with *Rotarix*® would prevent 13,164 severe cases and 3,478 deaths (Table 5).

Table 5. Number of cases averted with a universal vaccination against rotavirus with *Rotarix*®

Health states	No vaccination	Vaccination	Difference (No. of cases averted)
Mild (home care)	719,871	345,538	374,333
Moderate (GP visit)	158,331	71,249	87,082
Severe (hospitaliza-tion)	16,353	3,189	13,164
Death	4,190	712	3,478

In this study, rotavirus vaccination using *Rotarix*® with an assumed coverage of 100% for a cohort of about 2 million newborns in a year was estimated to have a gain of 240,731 undiscounted QALYs, or 102,298 discounted QALYs in comparison with no vaccination program.

Introduction of *Rotarix*® into the Expanded Programme of Immunization was estimated to result in an increase in overall costs of PHP 1,233,568,466 (from the societal perspective). From the payer perspective, the increase in cost was PHP 1,312,954,375 (Table 6).

From a payer perspective where only direct medical costs were included, the ICER was estimated to be PHP 12,835/QALY. With the inclusion of both direct non-medical costs (diapers and transport) and indirect costs from a societal perspective, the ICER improves to PHP 12,059 /QALY i.e. one QALY could be achieved at a lower cost.

Sensitivity Analyses

The univariate sensitivity analysis is summarized in Figure 2. The ICER varied most with the values of the probability of mild diarrhea, probability of moderate diarrhea, followed by the vaccine cost. These three parameters therefore represent the

Table 6. Results from base case analysis: no vaccination vs. vaccination (PHP)

Outcome measure	Vaccination	No vaccination	Vaccination vs. No vaccination
Costs			
Direct medical costs	1,721,373,899	408,419,524	1,312,954,375
Direct non-medical costs	29,112,089	67,108,059	(37,995,970)
Indirect costs	26,426,696	67,816,635	(41,389,939)
Total			
payer perspective	1,721,373,899	408,419,524	1,312,954,375
societal perspective	1,776,912,684	543,344,218	1,233,568,466
QALYs			102,298
Cost per QALY gained			
payer perspective			12,835
societal perspective			12,059

key uncertainty drivers for the cost effectiveness of a UMV vaccination program with *Rotarix*® versus no vaccination program in local context of the Philippines. This could be explained by the relatively lower diarrhea management costs e.g. visits to GP, other direct medical costs compared to the vaccine acquisition cost in the Philippines and high vaccine protection against rotavirus associated gastroenteritis given by a universal rotavirus vaccination program. As expected, income per day for productivity loss estimation is

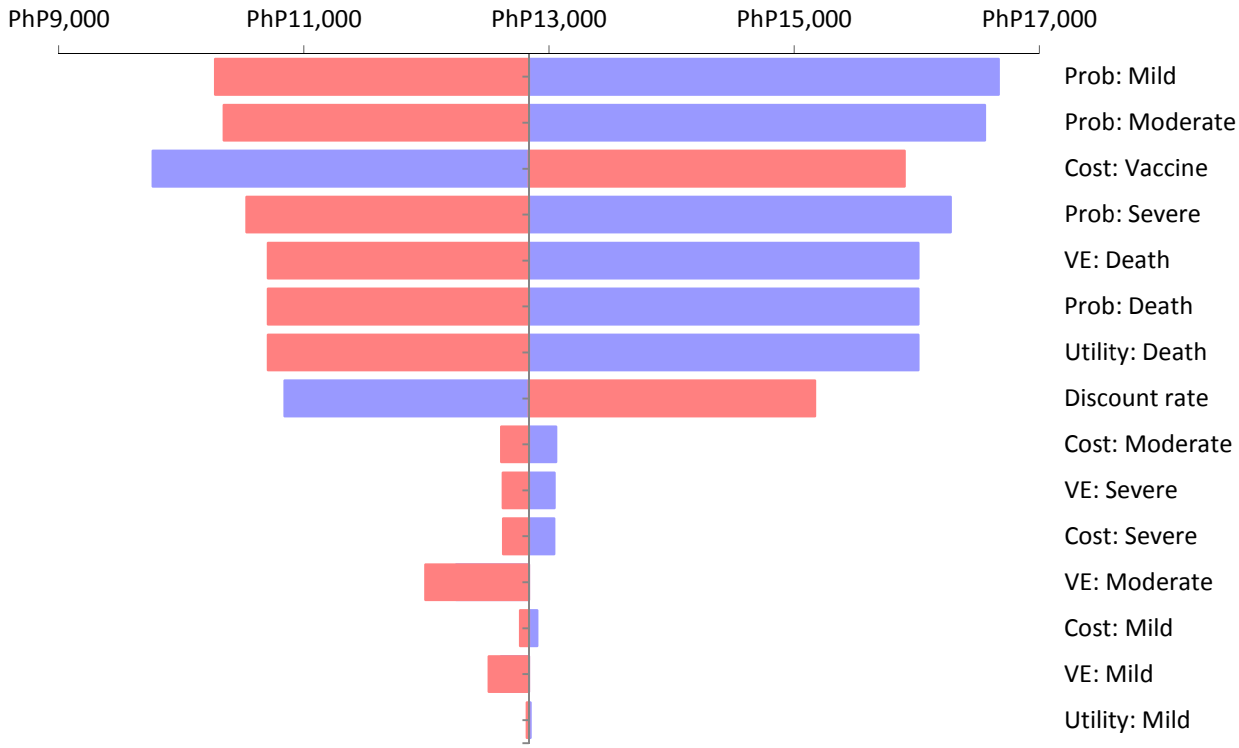

Figure 2. Results of univariate sensitivity analyses

not the main driver of uncertainty given the small number of days i.e. 1 day for moderate diarrhea state and 3 days for severe diarrhea state were incurred for the caregivers to stay at home.

The resulting ICERs of the scenario analyses range between PHP 949/QALY and PHP 77,398/QALY and between PHP 78 and PHP 75,534/QALY from the payer and societal perspectives, respectively

DISCUSSION

Under the WHO's recommendation on cost effectiveness threshold of three times the GDP, rotavirus vaccination is projected to be *very cost-effective* in the local context of the Philippines in comparison with no vaccination. All the ICERs in the base case, univariate and multivariate sensitivity analyses were well below PHP 310,098 (3 times the 2012 GDP in the Philippines of PHP 103,366). This result is in line with findings from other Asia Pacific countries which have also found rotavirus vaccination to be cost-effective when compared with the current situation of no vaccination using a variety of modeling techniques.[15, 29-33] Depending on the price of the vaccine and local disease burden, the vaccine could become cost-saving in these countries, as is the case for Indonesia[14].

The Philippines is the first Southeast Asian country which has included rotavirus vaccination as per WHO recommendations in its Expanded

Programme of Immunization, with selective vaccination for the very poor as defined by the National Housing Targeting System for Poverty Reduction (n=700,000)[34-37]. The results presented here provide evidence supporting the need to expand the program to cover the entire birth cohort. In addition to potential improvements in health, through this simple decision tree based modeling analysis, *Rotarix*® vaccination was found to be very cost-effective when compared to no vaccination, providing economic justification to support the introduction of rotavirus vaccination in the Philippines Expanded Programme of Immunization. As of 2013, Thailand is in the process of investigating the inclusion of rotavirus vaccination in their National Immunization Programme (NIP), with a regional pilot currently ongoing.[34] The Philippines is also embarking on an impact study to assess the effectiveness of rotavirus vaccination (personal communication with Philippines Department of Health). With increasing global financial support to eligible lower-middle-income countries such as the Philippines, more children would benefit from rotavirus vaccination program worldwide.[38, 39] Local health economic studies to assess the cost and benefits of rotavirus vaccination program versus no program provide useful information to assist in making a decision.

While the current decision tree model for comparing vaccination versus no vaccination is not designed to assess the difference between two-dose and three-dose vaccine regimens, when compared to the three-dose regimen, it is projected that the two-dose vaccine regimen would be preferred given that it is one fewer dose (and hence there would be no need for concerns regarding low compliance to the third dose), and there is also a monetary benefit for the two-dose as the costs of vaccine administration would be lower with a two-dose vaccine regimen. Furthermore, there is a better response after the first dose of a two-dose vaccine when compared with a three-dose vaccine as full protection is achieved sooner according to the respective vaccination dosing schedule. The vaccine efficacy after a first dose of a two-dose vaccine regimen is higher than that of a three-dose vaccine and it is the first exposure to the virus is most important as it causes more severe infection[40] despite some studies tend to suggest no clear distinction in vaccine efficacy overall in mild, moderate, and severe cases between a two-dose and a three-dose vaccine regimens.[41] Seroconversion rate may also be dependent on the interval between vaccination doses. In a study done in the Philippines, seroconversion rates at one month after the second dose were found to be higher in infants who received the doses one month apart, when compared to infants who received the doses two months apart.[42] Therefore, a vaccine that gives better protection at first dose should result in earlier protection against the disease.

There are a number of limitations that may affect the cost effectiveness results, stemming from the various simplifying assumptions made: First, the model does not account for the breastfeeding effect although there has been evidence that maternal antibodies are protective against rotavirus infection.[43-46] Second, nosocomial and community-acquired rotavirus gastroenteritis were not separately accounted for; impact studies have shown that the vaccine effect on nosocomial infection could be higher[47] and thus improve the cost-effectiveness result. Third, due to the limited evidence on estimating herd effect in this setting, a conservative approach was taken by omitting herd effects,

although its inclusion would also improve the ICER. In the absence of 100% vaccine coverage, such interactions would be of even higher importance. Fourth, compliance to complete a full vaccination schedule remains a challenge in many developing countries. Therefore it is recommended in future analysis to evaluate the trade-off between vaccine protection loss and reduction in vaccination cost due to compliance issue when data is available. Finally, there is usually an unequal spread of rotavirus disease over age as disease burden is higher in young children[48-51], so more complex modeling than a linear decrease of rotavirus gastroenteritis events as a function of age would be preferable.

Despite the limitations associated with the simple model, a recent analysis[10] compared the results of an advanced model with a simpler model such as the decision tree used in this study and found that both models reached similar conclusions, which indicates that simple models can be useful for countries that have limited data availability, such as the Philippines.

There is a caveat to the results in that disparities within the country are often not addressed through cost-effectiveness analyses. Poor regions of developing countries usually have limited financial resources, and thus there would likely be limited cost offsets through the introduction of vaccines due to limited facilities and resources in the first place to manage gastroenteritis cases that requires medical care at both GP and hospital levels. However, the poor regions are also likely to be the ones facing the highest burden of disease, so vaccination is likely to be very cost-effective yet there is no available budget. On the other hand, large variation in affordability as measured by GDP per capita across different regions or cities in a same country may render a vaccine cost effective in only certain regions thus sometimes making a national reimbursement listing and pricing of the vaccine a challenge. An additional consideration for developing countries comes in the form of maintaining the cold chain and logistics necessary for an effective introduction of a new vaccine, issues which may be difficult to quantify and hard to capture fully in a cost-effectiveness analyses.

This study is a first step to quantifying the economic impact of introducing rotavirus vaccination in the Philippines as well as potential drivers influencing cost-effectiveness given currently available data. Simplified assumptions were made as there were insufficient data for a comprehensive analysis. At the same time, the need for more comprehensive and accurate data inputs may further highlight the importance of more rigorous data collection systems, suggesting a clear direction for future research.

CONCLUSION

We conclude that a UMV program with *Rotarix*® vaccination in the Philippines may result in a significant improvement to public health, with the prevention of estimated 374,333 mild cases, 87,082 moderate cases of rotavirus related diarrhea cases, 13,164 severe cases and 3,478 deaths. Furthermore, it is very cost-effective from both the payer and the societal perspectives.

Trademarks

Rotarix® is a registered trademark of the GlaxoSmithKline.
RotaTeq®, is a registered trademark of Merck & Co., Inc.

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Authors' contributions

Baudouin Standaert and Carmen Nievera conceived the study. All authors contributed towards the data collection, analyses and interpretation of results.

Competing interests

I-Heng Lee, Baudouin Standaert, and Carmen Nievera are employees of GlaxoSmithKline. JR received an honorarium for her time spent on this study. All authors declare that they have no other competing interests. IMS Health Asia received payment for the writing of this manuscript.

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