Title: Cost-Effectiveness of Norovirus Vaccination in Children in Peru

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ABSTRACT

Background. With candidate norovirus (NV) vaccines in a rapid phase of development, assessment of the potential economic value of vaccine implementation will be necessary to aid health officials in vaccine implementation decisions. To date, no evaluations have been performed to evaluate the benefit of adopting NV vaccines for use in the childhood immunization programs of low- and middle-income countries.

Methods. We used a Markov decision model to evaluate the cost-effectiveness of adding a two-dose NV vaccine to Peru's routine childhood immunization schedule using two recent estimates of NV incidence, one for a peri-urban region and one for a jungle region of the country.

Results. Using the peri-urban NV incidence estimate, the annual cost of vaccination would be \$13.0 million, offset by \$2.6 million in treatment savings. Overall, this would result in 473 total DALYs averted; 526,245 diarrhea cases averted; 153,735 outpatient visits averted; and 414 hospitalizations averted between birth and the fifth year of life. The incremental cost-effectiveness ratio would be \$21,415 per DALY averted; \$19.86 per diarrhea case; \$68.23 per outpatient visit; and \$26,298 per hospitalization. Using the higher jungle NV incidence rates provided a lower cost per DALY of \$10,135. The incremental cost per DALY with per-urban NV incidence is greater than three times the 2012 GDP per capita of Peru but the estimate drops below this threshold using the incidence from the jungle setting. In addition to the impact of incidence, sensitivity analysis showed that vaccine price and efficacy play a strong role in determining the level of cost-effectiveness.

Conclusions. The introduction of a NV vaccine would prevent many healthcare outcomes in the Peru and potentially be cost-effective in scenarios with high NV incidence. The vaccine cost-effectiveness model could also be applied to the evaluation of NV vaccine cost-effectiveness in other countries. In resource-poor settings, where NV incidence rates are expected to be higher.

KEYWORDS

norovirus, caliciviruses, diarrhea, gastroenteritis, vaccine, cost-effectiveness, Peru, LMIC

INTRODUCTION

Diarrhea remains one of the largest causes of preventable death and disability among young children in low- and middle-income countries [1]. Prior to the introduction of vaccines against rotavirus, 1.4 billion children younger than five years of age developed diarrhea annually in these settings [2]. Of those, 123.6 million required medical care, and nine million were hospitalized [2]. While rotavirus vaccination has had an impact in terms of reducing child mortality, diarrhea remains a significant contributor to medical costs and morbidity in resource poor settings [3]. Interventions targeting the major etiologies of diarrhea in the children most susceptible to diarrhea-associated morbidity should accelerate the declining burden of disease.

Peru is a rapidly developing country with a current population of 30 million [4]. In 2009 it added a two-dose monovalent oral vaccine against rotavirus to its national immunization schedule, achieving annual national vaccine coverage rates of 95% and 86% for the first and second doses, respectively [5]. However, diarrhea-associated child morbidity in this setting remains significant [6]. Current evidence indicates that NV has become the number one cause of viral gastroenteritis in young children in

Peruvian communities, with over 70% of children in peri-urban communities experiencing between one and eight episode of NV diarrhea in the first two years of life [6]. In the wake of Peru's successful rotavirus vaccine implementation, NV has also been associated with over a third of cases of diarrhea in young children seeking hospital care for diarrhea [7]. This makes it one of the predominant pathogens in medically attended pediatric diarrhea cases, which can translate into substantial costs [8].

The development of an NV vaccine has been complicated in the past by the lack of a NV cell culture system, the heterogeneity of NV strains, and a lack of knowledge about cross strain immunity or the duration of protection conferred by NV infection. However, with the successful application of virus-like particle (VLP)-based vaccine technology for the highly effective Gardasil and Cervarix vaccines for human papillomavirus infections and precancerous lesions, there is promise that this same approach could be used as a template for NV vaccine development. Expression of the NV capsid proteins in eukaryotic cells leads to the spontaneous assembly of VLPs, which have been shown to be immunogenic when delivered parenterally, orally, or intranasally [9]. In 2011, a human trial of intranasally delivered, VLP-based vaccine against the prototypic Norwalk virus demonstrated 47% effectiveness against the vaccine strain [9]. Multivalent candidate vaccines against NV are currently under development, and other vaccine approaches include multivalent alpha-virus replicon particles (VRPs), that allow formation of NV VLPs, edible vaccines that deliver VLPs, P particle based vaccines, and polyvalent NV P domain glutathione S-transferase complexes [10].

With candidate NV vaccines in a rapid phase of development [11], assessment of the potential economic value of vaccination will be necessary to aid health officials in implementation decisions. Although previous analyses have found NV vaccines to be potentially cost-effective for outbreaks and in children younger than five years old in high-income countries [12, 13], no evaluations have evaluated the benefit of adopting NV vaccines for routine use in the childhood immunization programs of low- and middle-income countries. Here, we evaluate the cost-effectiveness of incorporating a vaccine against NV into the Peruvian national immunization schedule. A full-scale introduction of the vaccine is assumed and compared with a status quo scenario in which there is no national NV vaccination. Our model provides a useful template for evaluating the potential economic benefit of NV vaccine implementation in other resource-limited countries following the implementation of rotavirus vaccines at high coverage rates.

METHODS & DATA

We evaluated NV vaccine cost-effectiveness in a hypothetical cohort of children younger than five years of age in Peru. The evaluation used a five-year time horizon to estimate the incremental costs and health benefits of routine NV vaccine introduction compared with the status quo, where no NV vaccine was available, but rotavirus vaccination had been implemented at scale. We modeled the introduction of a vaccine against NV for the 2012 Peruvian birth cohort with an 85% vaccine coverage rate, which is similar to the scaled up rotavirus vaccine coverage rate in Peru in 2009 [1]. We reported costs in 2012 USD, and health effects as NV-associated diarrhea cases, outpatient visits, hospitalizations, deaths, and disability adjusted life years (DALYs) averted.

A Markov Model for CEA

We constructed a probabilistic three-box Markov model for the Peruvian birth cohort using TreeAge Pro software [14]. The basic model included a healthy state (no diarrhea) and a sick state (having diarrhea) (Figure 1). The third state was an absorbing state (cannot exit) for those that die. The model used a one-

month time step for the Markov process and ran for 60 months until the cohort reached the end of the fifth year of life. The entire birth cohort began in the healthy state and had a probability of transitioning to the NV diarrhea state based on the one-month hazard of NV diarrhea. Those who weren't infected with NV were also subject to the background hazard of mortality, which was the mortality rate from all non-NV causes. In the NV diarrhea state, children could either die from the NV-attributable hazard of mortality or recover to the healthy state in the next time step. Children in the absorbing state entered through either NV mortality or background mortality. At each time step, children who did not transition out of the healthy state remained there until the next month and were subject to the same probabilities for subsequent time steps.

Epidemiology and Effects Data

To model health effects, we used recently published data for the incidence of NV diarrhea from a community-level study in a peri-urban area of Lima [6]. For children 0-5, 6-11, and 12-24 months of age, the incidence was 2.4, 6.6 and 7.0 cases per 100 child-months, respectively. We also performed the analysis using recent data collected from an ongoing rural jungle diarrhea surveillance site in the Amazon Basin [15-17]. With these estimates, children aged 0-5 months, 6-11 months, 12-17 months, 18-24 months, 25-35 months, 36-47 months, and 48-59 months, experienced an incidence of 3.6, 15.8, 15.1, 8.6, 7.9, 6.8, and 5.5 cases per 100 child-months, respectively. In order to model the incidence out to 5 years (60 months), we assumed, based on Demographic Health Survey estimates and previous rotavirus modeling, that the pathogen-specific diarrhea incidence at 60 months was half of that at 12-24 and declined linearly with time [18, 19]. To estimate the distribution of NV severity, we used a global estimate of the proportion of NV diarrhea cases that are severe of 0.5%. This is much lower than estimates that have been used previously for rotavirus diarrhea, but is consistent with the clinical presentation of NV [20, 21].

Only severe NV diarrhea cases were at risk for NV specific mortality. We were not able to find NV diarrhea case fatality rate estimates for Peru or for other low and middle-income countries, so we estimated the NV case-fatality rate by calculating the annual NV deaths in children, taking the total diarrhea-attributable deaths in Peru, and multiplying this number by the percentage of deaths explained by NV. There were an estimated 429 all-cause diarrhea deaths in Peru in 2010, and a recent study reported that 13.6% of all diarrhea deaths in the Americas region were attributed to NV [1, 22]. We thus estimated that there were approximately 58 yearly deaths due to NV in 2012, and we divided this by the yearly NV diarrhea prevalence to obtain the case-fatality rate. We applied the 2010 estimate of NV mortality to the year 2012 with the assumption that any decline in overall diarrheal mortality between 2010 and 2012 was attributable to decreases in rotavirus-associated deaths.

In the arm of the model where vaccine was introduced, we assumed that vaccine effectiveness would reduce NV diarrhea incidence by 47% based on previous evidence from a trial in the United States [9]. This effectiveness is lower than the 65% effectiveness that was used for previous modeling of the impact of Rotavirus vaccine but reflects the fact that Rotavirus and NV vaccines are different in how they are made [23]. Additionally, given that the previous study from the United States was in a highly-controlled setting, we believe the 47% estimate may be lower in a real-world setting. To account for this, we also model a large uncertainty range around the effectiveness estimate in later sensitivity analyses.

Healthcare Resource Use

As in a previous rotavirus vaccine cost-effectiveness model for Peru, we estimated healthcare utilization only for the government-level facilities. The model uses the same healthcare resource utilization rates reported in the previous rotavirus vaccine cost-effectiveness analysis [23]. Non-severe cases and severe cases visited outpatient centers 29.1% of the time; however, 15.1% of severe cases also visited an inpatient center. We assumed that there was no overlap in the use of health care facilities, meaning the same patient would not visit more than one facility for care during a single diarrhea episode, and that those patients who did not visit any facility sought no care or sought care from the private sector. In the model, outpatient-level visits for both severe and non-severe cases took place at government clinics and primary, secondary and tertiary government hospitals. For the severe cases, inpatient-level visits only occurred at primary, secondary or tertiary government hospitals. We assumed that the case fatality for severe NV diarrhea cases was the same regardless of the type of facility used.

Cost Data

To determine the total annual vaccine costs and treatment savings, we used the Peruvian under five population in 2012 and assumed that vaccine coverage was scaled up to 85% coverage for a 2-dose schedule [24, 25]. As no NV vaccines are currently on the market, we used current cost estimates of another VLP-based vaccination, the human papilloma virus (HPV), from PAHO's Revolving Fund and from a separate study in Brazil [26, 27]. This resulted in a cost of \$13.19 per dose and a 2-dose cost of \$26.44 when accounting for syringe costs. Assuming that the vaccination would be added to the current routine system and that there is adequate capacity, we did not include any incremental personnel and cold chain costs since they would be minimal. We also assumed that there would be minimal vaccine wastage and no adverse effects. We accounted for treatment costs related to healthcare resource during outpatient and inpatient visits based on previous work for rotavirus that collected health care resource information from the Peruvian government [23]. These costs were broken down into outpatient and inpatient-level costs and used as weighted averages of urban and rural treatment costs, with 78% of the Peruvian population residing in urban areas in 2012 (Table 1) [24].

Sensitivity Analyses Methods

We tested the model using key variables in multiple one-way deterministic sensitivity analyses and in a two-way sensitivity analysis with key parameters. We also performed a probabilistic sensitivity analysis using a Monte Carlo simulation with 20,000 draws, inputting distributions according to the parameter expected value and standard deviation based on each parameter's uncertainty distribution (Table 1). Taking independent draws from each distribution, we then evaluated the output distribution of the cost per averted DALY across a range of willingness to pay thresholds.

RESULTS

Our model found that if a 2-dose NV vaccine was introduced and scaled up in Peru's routine childhood immunization system, the cost per DALY averted would be \$21,415 (Table 2). The World Health Organization (WHO) Commission on Macroeconomics and Health defines an intervention as being "very cost-effective" if it costs less than the gross domestic product (GDP) per capita of a country and "cost-effective" if it is less than three times the GDP per capita [28]. Given that Peru's GDP per capita was \$6,424 in 2012, we found the introduction of NV vaccine was not cost-effective at the baseline conditions [29]. A birth cohort vaccinated at 85% vaccine coverage as described would result in 473 total DALYs; 526,245 cases of diarrhea; 153,735 outpatient visits; and 414 hospitalizations averted between

birth and the fifth year of life (Table 3). The cost-effectiveness was found to be \$19.86 per diarrhea case averted; \$68.23 per outpatient visit averted and \$26,298.7 per hospitalization averted (Table 2). The annual cost of vaccination would be \$13.0 million, offset by \$2.6 million in treatment savings (Table 2).

Compared with NV diarrhea incidence rates from the peri-urban setting, the higher rural jungle incidence rates (Table 1) provided more favorable cost-effectiveness estimates: \$10,135 per DALY averted; 828 total DALYs averted; 910,581 diarrhea episodes averted; 266,079 outpatient visits averted; and 710 hospitalizations averted (Table 2). The same annual \$13.0 million cost of vaccination would be offset by \$4.5 million in treatment savings (Table 2). When we varied the incidence rates according to the highest and lowest values for specific age strata in each setting (Table 3), the cost per DALY averted ranged from \$15,616 to \$41,512, respectively, in the peri-urban and from \$4,483 to \$14,700, respectively, in the rural jungle setting.

Parameter Sensitivity Analyses

In one-way sensitivity analysis, we varied the cost of vaccination and vaccine effectiveness to examine how the resulting change in cost per DALY averted. The maximum estimated cost per DALY averted was around \$12,500 in the rural jungle and under \$24,500 in the peri-urban setting (Figure 2A). When vaccine effectiveness was optimized to around 90%, the cost per DALY averted was around \$8,000 with peri-urban incidence estimates and dropped below \$2,500 with rural jungle incidence estimates (Figure 2B). The multiple one-way deterministic sensitivity analyses demonstrated that vaccination cost and vaccine efficacy were the two most influential model variables (Appendix Figure 1A and 1B). The proportion of patients accessing outpatient care and the cost of outpatient care for non-severe cases were the next most influential model variables; which makes sense because of the majority of non-severe cases. Due to the low proportion of NV diarrhea cases that result in death and inpatient hospitalization, these two model variables were the least influential.

Results of two-way sensitivity analysis were produced to show the interaction between vaccine cost and vaccine efficacy (Appendix 1A and 1B) for the peri-urban incidence scenario. Using a willingness to pay threshold of one times the GDP per capita, it is seen that the vaccine would have to be at least 70% effective at the lowest vaccine cost of \$17.06 (or \$8.50 per dose) to be considered cost-effective. At a vaccine cost of around \$22.46 (\$11.20 per dose), the vaccine effectiveness would have to be greater than the highest estimate of 91% to be considered cost-effective. With a threshold of three times the GDP per capita, however the vaccine would need to be 35% effective at the lowest cost per dose and 55% effective at the highest cost per dose to be considered cost-effective.

The probabilistic sensitivity analysis of the model parameters demonstrated that NV vaccination had an approximately 30% chance of being cost-effective at the 2012 GDP per capita threshold in the peri-urban case (Figure 3). Using the jungle incidence, NV vaccination is cost-effective 50% of the time using a GDP per capita threshold.

DISCUSSION

Our results suggest that vaccinating young children against NV could offer economic value under the right conditions in Peru by averting poor health outcomes and substantial healthcare utilization.

Our model provides conservative estimates of the potential economic benefits of a NV vaccine. The model did not include indirect costs of NV infection, nor did it include any additional direct costs for self-

treatment or home care. These costs are expected to be significant, and including them would further augment the economic value of a NV vaccine [7]. Likewise, the model did not account for indirect benefits attributable to reduced shedding in the community, herd immunity produced by widespread vaccination, or reduced disease transmission to older children and adults. As demonstrated by the mucosal immunity and decrease in shedding of virus after oral poliovirus immunization relative to inactivated poliovirus immunization, the indirect vaccine benefits attributable to mucosal and herd immunity may be greater if a candidate NV vaccine is oral or intranasal rather than injectable [30]. The model also did not quantify the interaction of diarrhea and malnutrition, even though NV infection during the first year of life is associated with linear growth deficits [6]. With the reduction in infections brought about by vaccination, we would expect the population-level nutritional profile to improve, resulting in additional health, social, and economic benefits that would enhance the vaccine's cost-effectiveness. In rural populations, delays in seeking, reaching, and receiving adequate care in rural areas could lead to poor outcomes and increased health costs, the prevention of which would further enhance the potential benefits of vaccination. The increased incidence of diarrhea in the rural jungle population is likely a reflection of decreased sanitation levels, and thus would be more comparable to incidence rates in less developed settings. Health care utilization rates were based on Demographic Health Surveys, which are prone to underestimation, thus providing a conservative estimate of care seeking associated with diarrhea. Our estimates of the inpatient cost per bed-day (\$16-63 in 2012) were comparable to estimates from WHO Choosing Interventions that are Cost-Effective (\$43-58 during 2008) [28]. Our estimates for outpatient visit costs (\$2-6 in 2012) were more conservative than WHO estimates (\$6-9 during 2008) [28]. As access to and cost of medical care continue to increase in Peru over time, we expect the estimated value of a potential vaccine to increase as well.

Our model relied on estimates of NV incidence, diarrhea severity, and healthcare utilization in order to determine vaccine cost-effectiveness. The application of this model to other low- and middle-income settings will require accurate estimates of these parameters. However, the global literature does not uniformly measure the burden of NV disease in terms of incidence, severity, or healthcare utilization. For example, the Global Enteric Multicenter Study (GEMS), which aimed to identify the etiology and population-based burden of pediatric diarrheal disease in sub-Saharan Africa and South Asia, defined its "moderate-to-severe" diarrhea inclusion criterion as an episode in a child with at least one of the following: sunken eyes, loss of skin turgor, prescription or administration of intravenous fluids, dysentery, or hospital admission [31]. This case definition biased selection away from NV-associated diarrhea cases despite evidence from a Chilean cohort study that almost half of NV infections caused moderate-to-severe diarrhea when defined using a Vesikari scale in which a scores of 0-6, 7-11, and 12-20 represented mild, moderate, and severe disease, respectively [32]. Future evaluations of NV disease burden should include associated medical expenditures, indirect cost estimates, and population-level nutritional parameters, in addition to using similar case definitions and diarrhea severity scales.

We further stress the importance of understanding diarrhea etiology and the role of NV as well as other pathogens. In high income settings with low rates of rotavirus, it has been shown that the prevalence of caliciviruses in medically attended diarrhea is quite high [8]. Globally, other pathogens, such as cryptosporidium, are highly prevalent in children with acute diarrheal disease [31]. However, the low prevalence of cryptosporidium among children in Peru may be due to the relatively higher level of economic development and lower rates of HIV and malnutrition in this setting [33]. A 2004 study from Peru for instance showed that NV was the predominant pathogen found in stools of children

hospitalized with diarrhea [34], while a 1999 study detected cryptosporidium in less than 5% of stools from children with diarrhea [33]. Although it is less severe than rotavirus, one reason why norovirus may be an attractive target for vaccine development is due to the high prevalence seen in diarrhea hospitalization.

Our model made a number of simplifying assumptions due to available data limitations and cannot represent every possible outcome. It also could not capture all of the heterogeneities among Peruvian communities. Data used in our model came from various studies of differing quality, and uncertainty underlies our parameter estimates; therefore, results may change as more data become available. Data gaps regarding the profile of a NV vaccine remain, including vaccine efficacy, protection duration, safety, and cost. Vaccine trials should assess the duration of vaccine-induced immunity and cross-protection against prevalent NV genotypes and variants. The genetic diversity of circulating strains and the degree to which a vaccine could protect against genetically drifting, shifting, and emergent pandemic NV strains remain important considerations. To an extent, we have considered these uncertainties through sensitivity analyses, and as additional data on vaccine performance from clinical trials become available, our model estimates can be further refined.

Our sensitivity analyses demonstrate that NV vaccine implementation may be considered cost-effective in settings when the cost of vaccination is low or vaccine efficacy is high. In such cases, when the model parameters for incidence, vaccination costs, and/or vaccine efficacy produce results close to the decision threshold, determining whether the benefits of vaccine implementation outweigh the costs becomes less clear [35]. Based on Peru's GDP per capita, a decision threshold that has been challenged in the literature, the potential of a NV vaccine to avert outpatient health services make implementation favorable despite the low baseline incidence of NV-specific mortality. However, when the cost-effectiveness of an intervention is equivocal, health policy and decision-makers may take 'other' criteria into account, such as whether the benefits to society outside those considered in the model might make vaccine implementation socially desirable. Alternately, cost-effectiveness might be achieved by appropriately targeting high-incidence sub-populations or vaccinating against NV during outbreaks, which has proven cost-effective in high-income under-five populations [12].

CONCLUSION

In conclusion, this model, which can be applied to the evaluation of NV vaccine cost-effectiveness in other resource-limited settings, found routine childhood vaccination against NV provides many health and healthcare benefits, but that at the population level, the cost-effectiveness in Peru is not certain based on current knowledge and World Health Organization guidelines.

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Table 1. Norovirus Cost-Effectiveness Analysis Parameters

Parameter	Model Value	Uncertainty Range	Distribution	Source
<i>Epidemiology</i>				
Birth Cohort Size	591,287	--	--	UNPP 2012 [25], World Bank 2014 [24]
Vaccine Coverage (%)	0.85	0.6 - 0.99	--	WHO 2014 [5]
Vaccine Effectiveness (%)	0.47	0.21 - 0.91	Beta	Atmar 2011 [9]
Peri-Urban NV Incidence (per 100 child-months) Stratified by Age Group (in months of age)				Saito 2014** [6]
0-5 months	2.4	1.7 – 3.4	Beta	
6-11 months	6.6	2.1 – 8.0	Beta	
12-23 months	7.0	6.1 – 8.4	Beta	
24-35 months	3.5	1.5 – 4.8	Beta	
36-47 months	3.0	1.0 – 4.3	Beta	
48-59 months	2.6	0.6 – 3.9	Beta	
60 months	2.1	0.1 – 3.4	Beta	
Rural Jungle NV Incidence (per 100 child-months) Stratified by Age Group (in months of age)				Yori 2013 [15]
0-5 months	3.6	2.6 – 17.0	--	
6-11 months	15.8	13.3 – 18.9	--	
12-17 months	15.1	12.4 – 18.4	--	
18-24 months	8.6	6.5 – 11.3	--	
24-35 months	7.7	5.7 – 13.4	--	
36-47 months	6.0	4.0 – 11.7	--	
48-59 months	4.3	2.3 – 10.0	--	
60 months	2.6	0.6 – 8.3	--	
% Severe NV Diarrhea	0.5%	0.25% - 1%	Beta	Lamberti 2012 [20]
NV Case-Fatality Rate	0.0061%	0.0031% - 0.012%	Beta	Liu 2012 [1], Lanata 2013 [22]
<i>Utilization & Access</i>				
Urban	78%	--	--	World Bank 2014 [24]
Rural	22%	--	--	World Bank 2014 [24]
Outpatient Access (any severity)	29.1%	26.2 - 32.0	Beta	Clark 2009 [23]

Inpatient Access (severe only)	15.1%	13.6 - 16.6	Beta	Clark 2009 [23]
Outpatient utilization (any severity)				
Government Clinic	51.8%	46.6 - 57.0	Dirichlet	Clark 2009 [20]
Government Primary Hospital	27.3%	24.6 - 30.0	Dirichlet	Clark 2009 [20]
Government Secondary Hospital	20.7%	18.6 - 22.7	Dirichlet	Clark 2009 [20]
Government Tertiary Hospital	0.24%	0.22 - 0.27	Dirichlet	Clark 2009 [20]
Inpatient Utilization (severe only)				
Government Primary Hospital	59.6%	53.7 - 65.6	Dirichlet	Clark 2009 [20]
Government Secondary Hospital	40.0%	36.0 - 44.0	Dirichlet	Clark 2009 [20]
Government Tertiary Hospital	0.41%	0.37 - 0.45	Dirichlet	Clark 2009 [20]
Costs (2012 USD)				
Vaccine Cost (2 doses)	\$26.44	\$17.06 - \$29.06	Lognormal	[26, 27]***
Outpatient Non-Severe				
Government Clinic	\$14.91	\$13.42 - \$16.40	--	Clark 2009 [20]
Government Primary Hospital	\$20.53	\$18.48 - \$22.58	--	Clark 2009 [20]
Government Secondary Hospital	\$19.74	\$17.77 - \$21.71	--	Clark 2009 [20]
Government Tertiary Hospital	\$72.82	\$65.54 - \$80.10	--	Clark 2009 [20]
Outpatient Severe				
Government Clinic	\$26.05	\$23.45 - \$28.66	--	Clark 2009 [20]
Government Primary Hospital	\$26.02	\$23.42 - \$28.62	--	Clark 2009 [20]
Government Secondary Hospital	\$43.65	\$39.29 - \$48.02	--	Clark 2009 [20]
Government Tertiary Hospital	\$72.82	\$65.54 - \$80.10	--	Clark 2009 [20]
Inpatient Severe				
Government Primary Hospital	\$158.86	\$142.97 - \$174.75	--	Clark 2009 [20]
Government Secondary Hospital	\$255.53	\$229.98 - \$281.08	--	Clark 2009 [20]
Government Tertiary Hospital	\$485.22	\$436.70 - \$533.74	--	Clark 2009 [20]

Abbreviations: NV—Norovirus; USD—United States Dollars

*Derived from the introduction of Rotavirus vaccination

** Saito 2014 report rates up to two years old and linear interpolation is used to obtain the rates for subsequent years

***2 doses at \$13.19 per dose plus \$0.03 per syringe

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Table 2. Total Vaccine Costs, Treatment Savings, Averted Outcomes, and Cost-Effectiveness (2012 USD)

Strategy	Vaccine Costs*	Treatment Savings	Total DALYs Averted	Total Cases Averted	Total Outpatients Averted	Total Hosp. Averted	Incremental Cost	Incremental DALY Averted	Incremental Cases Averted	Incremental Outpatient Visit Averted	Incremental Hospitalization Averted	Cost** per DALY Averted	Cost per Averted	Cost per Outpatient Visit Averted	Cost per Hospitalization Averted
Peri-Urban NV Incidence Rate [6] Vaccine vs No Vaccine	\$13,288,576.55	\$2,613,487.07	473	526,245	153,735	414	\$17.72	0.008	0.89	0.26	0.0007	21,415.95	19.86	68.23	26,298.70
Rural Jungle Incidence Rate [15] Vaccine vs No Vaccine	\$13,288,576.55	\$4,517,430.13	828	910,581	266,079	710	\$14.50	0.0014	1.54	0.45	0.0012	10,135.68	9.40	32.29	12,445.14

Abbreviations: NV—Norovirus; DALY – Disability Adjusted Life Years; USD – United States Dollars

Section 1: Cost, DALY, Cases, Outpatient Visits, and Hospitalizations represent the number of each outcome that a child is expected to experience between birth and the fifth year of life.

Section 2: Incremental Cost, DALYs Averted, Cases Averted, Outpatient Visits Averted, and Hospitalizations Averted represent the difference between each outcome that each child will incur between birth and the fifth year of life if a vaccination is implemented versus if no vaccination is implemented.

Section 3: Cost per DALY Averted, Case Averted, Outpatient Visit Averted, and Hospitalization averted for the whole birth cohort between birth and the fifth year of life.

*The vaccine costs here are the same because the incidences from each setting are applied to the entire population of children in Peru. Denoting ‘peri-urban’ and ‘rural jungle’ show the study where the incidences come from, however, given the uncertainty around the actual population-level incidence of norovirus, the varying estimates in these two studies serve as a sensitivity analysis of the actual incidence.

**Two doses, scaled up in the national childhood immunization program

Table 3. Sensitivity Analysis of Varying Norovirus Incidence Estimates Using Data from Peri-urban and Rural Jungle Settings.

	<i>Peri-Urban NV Incidence Rate [6]</i>			<i>Rural Jungle NV Incidence Rate [15]</i>		
	Peri-Urban Incidence Estimate	Lower Confidence Limit	Upper Confidence Limit	Rural Jungle Incidence Estimate	Lower Confidence Limit	Upper Confidence Limit
Incremental Cost	17.72	19.62	16.5	14.5	16.24	10.1
Incremental DALY Averted	0.0008	0.0005	0.0011	0.0014	0.0011	0.0023
Incremental Cases Averted	0.89	0.51	1.14	1.54	1.19	2.44
Incremental Outpatient Visit Averted	0.26	0.15	0.33	0.45	0.35	0.71
Incremental Hospitalization Averted	0.0007	0.0004	0.0009	0.0012	0.0009	0.0018
Cost per DALY Averted	21,415.95	41512.75	15,616.37	10,135.68	14,700.8	4,483.09
Cost per Case Averted	19.86	38.84	14.44	9.4	13.68	4.14
Cost per Outpatient Visit Averted	68.23	133.45	49.63	32.29	47.02	14.24
Cost per Hospitalization Averted	262,298.70	51,440.20	19,129.24	12,445.14	18,123.61	5,489.27

Abbreviations: NV—Norovirus; DALY—Disability Adjusted Life Years

Figure 1. Markov Decision Model for Norovirus Vaccination

Abbreviations: CEA – Cost-effectiveness analysis; NV - norovirus

Note: *Several branches have been collapsed to fit the figure (denoted with plus sign). Nodes with an 'M' denote a Markov process.*

346 **Figure 2A (top) and 2B (bottom). One-way sensitivity of Cost per Disability Adjusted Life Year (DALY) Averted**
347 **versus Vaccine Cost (2A, top) and Vaccine Effectiveness (2B, bottom) using Peri-urban [6] and Jungle [15]**
348 **Norovirus Incidence Rates.**

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Figure 3. Probabilistic Sensitivity Analysis Depicting the Proportion of the Distribution of Cost per Disability Adjusted Life Year (DALY) Averted that is Cost-Effective by a Range of Cost-Effectiveness Threshold Values, or “Willingness to Pay” (2012 USD).

Note: The World Health Organization Commission on Macroeconomics and Health defines an intervention as being “very cost-effective” if it costs less than one times the gross domestic product (GDP) per capita of a country [28]. For Peru, this threshold would be represented by a Willingness to Pay (x-axis) of \$6,242.

358 **Appendix Figure A1 Peri-Urban (top) and Figure A2 Jungle (bottom). Multiple One-way Sensitivity Analysis for**
359 **Key Variables.**

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361 WTP: willingness to pay in 2012 USD.

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363 **Appendix Figure B1 Peri-Urban (top) and Figure B2 Jungle (bottom). Two-way Sensitivity Analysis for Key**
364 **Variables.**

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366 WTP: willingness to pay in 2012 USD.

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Appendix Figure 1A and 1B

Appendix Figure 2A 2B ADD