



Cost-effectiveness of rotavirus vaccination in Bolivia from the state perspective

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Abstract

Background: In Bolivia, in 2008, the under-five mortality rate is 54 per 1000 live births. Diarrhea causes 15% of these deaths, and 40% of pediatric diarrhea-related hospitalizations are caused by rotavirus illness (RI). Rotavirus vaccination (RV), subsidized by international donors, is expected to reduce morbidity, mortality, and economic burden to the Bolivian state. Estimates of illness and economic burden of RI and their reduction by RV are essential to the Bolivian state's policies on RV program financing. The goal of this report is to estimate the economic burden of RI and the cost-effectiveness of the RV program. Methods: To assess treatment costs incurred by the healthcare system, we abstracted medical records from 287 inpatients and 6751 outpatients with acute diarrhea between 2005 and 2006 at 5 sentinel hospitals in 4 geographic regions. RI prevalence rates were estimated from 4 years of national hospital surveillance. We used a decision-analytic model to assess the potential cost-effectiveness of universal RV in Bolivia. Results: Our model estimates that, in a 5-year birth cohort, Bolivia will incur over US\$3 million in direct medical costs due to RI. RV reduces, by at least 60%, outpatient visits, hospitalizations, deaths, and total direct medical costs associated with rotavirus diarrhea. Further, RV was cost-savings below a price of US\$3.81 per dose and cost-effective below a price of US\$194.10 per dose. Diarrheal mortality and hospitalization inputs were the most important drivers of rotavirus vaccine cost-effectiveness. Discussion: Our data will guide Bolivia's funding allocation for RV as international subsidies change.

1. Introduction

Rotavirus is the leading cause of severe gastroenteritis among children under five years of age and is globally responsible for an estimated 111 million episodes of diarrhea requiring home care, 25 million clinic visits, 2 million hospitalizations, and as many as 592,000 deaths annually [1,2]. Children in low-income countries are disproportionately affected by rotavirus, accounting for more than 80% of these deaths [1,2]. The introduction of effective rotavirus vaccines is a promising intervention in preventing global diarrheal morbidity and mortality. However, the high cost of the new rotavirus vaccines, compared to relative costs of pennies per

dose for older vaccines, has resulted in limited implementation in low-income countries.

Estimates of the economic burden of rotavirus diarrhea vary substantially by country [3–30]. For example, adjusting by population, the annual per capita costs for treatment of rotavirus diarrhea ranged from US\$0.07 per person in the Dominican Republic [7] to over US\$0.97 per person in the United States [13]. Therefore, country-specific rotavirus cost-burden estimates are essential to assess the country-specific cost effectiveness of the rotavirus vaccine. Cost-effectiveness analysis (CEA) outcome measures permit standardized comparisons of cost-effectiveness across a range of health interventions. The results of published CEAs for rotavirus vaccination have varied. Out of 36 published studies, universal rotavirus vaccination was determined to be potentially cost saving in three studies [31–33], potentially cost-effective in 27 studies [3,4,6,13,29,30,32,34–52], unlikely to be cost-effective in six studies [53–58], and inconclusive in one study [59]. Estimates of costs per DALY averted ranged from US\$15.32 in middle-income Asian countries (vaccine price of US\$2 per course) [6] to US\$10,656 in

Table 1
Variables used in the cost-effectiveness and impact analyses.

Variable	Reference(s) for baseline estimate	Baseline estimate (range)	Distribution for uncertainty analysis ^a
Health			
Birth cohort	[64]	251,000	NA
Percent of <5 deaths due to diarrheal disease	[62]	0.15	NA
Diarrheal mortality rate/1000 live births	[62]	0.0081 (0.0073–0.0089)	±10% [34]
Health care			
Hospitalization rate of acute diarrheal disease (<5 years of age) in Birth cohort	[65]	0.94 (0.07–0.12)	±30%
Birth cohort			
Hospitalization length of stay	Study data	5	NA
Outpatient visit rate for acute diarrheal disease (<5 years of age) in Birth cohort	[65]	0.76 (0.53–0.99)	±30%
Birth cohort			
Proportion of hospitalized diarrhea cases with rotavirus	^b	0.40	NA
Proportion of outpatient diarrhea cases with rotavirus	^b	0.25	NA
Proportion of diarrhea deaths due to rotavirus	^c	0.40	NA
Vaccine efficacy			
Against severe rotavirus resulting in death	[72]	0.85 (0.51–0.871)	±2.5 [79], –40% [80]
Against severe rotavirus resulting in hospitalization	[72]	0.85 (0.51–0.897)	+5.5% [79], –40% [80]
Against rotavirus resulting in an outpatient visit	[50,72]	0.78 ^d (0.468–0.823)	+5.5% [79], –40% [80]
DPT coverage	[71]	0.44–0.88 (0.33–0.66–0.55–1.0)	±25% [37]
Cost data			
Outpatient costs	Study data	16.88 (12.39–20.65)	±25% [4,6,37,50]
Inpatient costs	Study data	260.57 (193.85–323.08)	±25% [4,6,37,50]
Cost of administration	[4,34,37,44,51,73]	0.50	NA

^a NA: not applicable, not included in one-way or multivariate models.

^b Local surveillance data from Bolivia's National Rotavirus Surveillance Program.

^c No reliable data exists so range assumed it equal to the equivalent hospitalized data.

^d Vaccine efficacy against cases requiring outpatient care was estimated to be the average of the efficacy against severe rotavirus illness (85%) and rotavirus illness of any severity (70%) [50].

Chile (vaccine price of US\$24 per course) [7]. The break-even price of the vaccine, defined as the price at which vaccination costs equal the costs saved by the health system, ranged from US\$0.18 in low-income Asian countries [6] to US\$54 USD in Taiwan [57].

While many Latin American countries have undertaken cost-effectiveness analyses to facilitate policy decisions regarding rotavirus vaccination, Bolivia remains an exception. Bolivia is one of the least developed countries in the Americas, with nearly 60% of the population living in conditions of poverty and nearly 25% living in conditions of extreme poverty [60]. The nation suffers from the region's highest rates of childhood mortality, and the World Health Organization (WHO) estimates that diarrhea is responsible for 15% of these deaths [61]. In 2008, Bolivia implemented a universal rotavirus vaccination campaign with financial support from The Global Alliance for Vaccines and Immunization (GAVI) through the year 2017. The goal of this paper is to fill gaps in knowledge regarding the economic burden of rotavirus and cost-effectiveness of the rotavirus vaccination program in Bolivia. The subsequent analysis provides data for decision makers regarding the projected economic impact of vaccination at a range of vaccine prices reflecting the dynamic market value of this vaccine.

2. Methods

2.1. Model

To calculate the cost-effectiveness of universal rotavirus vaccination in Bolivia, data were analyzed through an economic model developed by Rheingans et al. [44,51]. This decision model was created using Microsoft 2000 Excel software (Microsoft Corporation, Redmond, Washington) and compares the cost of universal rotavirus vaccination in Bolivia (intervention costs) with the hypothetical treatment costs of rotavirus diarrhea potentially

prevented by vaccination. Model inputs included country-specific economic, health systems, demographic and rotavirus epidemiology data, encompassing rotavirus disease morbidity and mortality, healthcare utilization and costs for rotavirus-associated events, and vaccination coverage (Table 1). The model examined cost-effectiveness from a health system point-of-view, and no data regarding societal costs borne by individuals (e.g. costs to fill prescriptions, work days lost, etc.) were included.

2.2. Rotavirus morbidity and mortality

Diarrheal mortality in children under 5 years of age and an estimate of annual diarrheal deaths in Bolivia was calculated using 2010 mortality rates from the World Health Organization (WHO) [62]. We assumed the proportion of diarrhea deaths due to rotavirus was the same as the proportion of hospitalized cases due to rotavirus, as etiological data was not available for diarrhea mortality. We estimated the five-year cumulative risk for hospitalization and outpatient care due to rotavirus disease based on administrative data from the National Statistics Institute of Bolivia [63], the 2003 birth cohort (251,000 consistent through 2009) [64], and data on the proportion of these events due to rotavirus, as identified by the National Rotavirus Surveillance Program (NRSP) in Bolivia (Table 1).

The rates of hospitalization and outpatient care for diarrheal diseases were calculated by dividing the annual number of hospitalizations and outpatient visits due to diarrhea (National Statistics Institute in Bolivia [65]) by the birth cohort (251,000) [64]. The proportion of hospitalized children with rotavirus diarrhea was obtained from data from Bolivia's National Rotavirus Surveillance Network. Within surveillance hospitals, rotavirus diarrhea was defined as a child whose inpatient stool tested positive for rotavirus with the OXOID ProSpecT™ Rotavirus EIA Kit test (Oxoid, United

Kingdom). The average length of stay for children treated for rotavirus in each type of facility was calculated from patient data collected as part of this study. A summary of the baseline inputs for the model is in [Table 1](#).

2.3. Study population

Data collection on treatment costs took place at five sentinel hospitals (Hospital Boliviano Holandes in El Alto, Hospital Materno Infantil and Hospital del Niño in La Paz, Centro Pediatría Albino R. Patiño in Cochabamba, and Hospital Mario Ortiz Suarez in Santa Cruz) participating in Bolivia's rotavirus surveillance program. These sites included both privately and publicly funded hospitals, and pediatric and general hospitals. Data was abstracted from inpatient and emergency department records of children less than 60 months of age treated for acute diarrheal disease.

The inpatient study population included a total of 287 patients admitted to the hospital for at least one night with diarrheal disease between August 1st, 2005 and August 30th, 2006. WHO guidelines for selecting an appropriate sample size suggest selection of every fifth patient with a diagnosis of acute diarrhea [66], however, we selected every third inpatient to ensure an adequate sample size. The outpatient study population included all 6751 patients who presented to the emergency departments of surveillance hospitals with acute diarrhea between January 1, 2006 and December 31, 2006. Outpatient records with missing data regarding treatment or diagnostics were removed from the database to avoid underestimation of direct medical costs. Exclusion criteria included age over 60 months, dysentery, or a note of suspected bacterial, parasitic, dietary or other non-viral cause of diarrhea. Patients with a comorbidity of pneumonia were also excluded to avoid the inclusion of costs not related to diarrhea treatment.

2.4. Cost data

Cost data was estimated from medical records data and previously published estimates. Only direct medical costs were included in the calculations of cost data.

2.4.1. Inpatient costs

We found a wide variation in hospital bed-day cost data both between hospitals and among patients at the same hospital based on insurance coverage. Despite protracted research and interviews with the hospitals accounting department and Ministry officials, we could not guarantee that hospital bed-day costs excluded government subsidies or used consistent pricing methodology. Therefore, for consistency across facilities and reliability of the price of a hospital bed-day to the state, we used WHO 2005 country-specific estimates of unit-costs for these patient services [67]. All hospitals in the study fit the WHO's definition of a tertiary hospital [68]; therefore, tertiary-level cost estimates were used for all inpatients and outpatients who received care in a hospital setting. These estimates account for costs such as personnel, capital, and food, but exclude diagnostics and medications.

Medications, medical equipment, and diagnostic tests ordered for inpatients were abstracted from pharmacy records and patient charts. Drug and medical equipment costs were estimated from Management Sciences for Health's (MSH) International Drug Price Indicator Guide [69] or the International Dispensary Association's (IDA) catalogue [70]. If a medication was not listed in either of these sources, Bolivia's government health insurance reimbursement rate for the given medication was used. Diagnostic costs were not available from either MSH or IDA; therefore Bolivia's government health insurance reimbursement rate was used. Costs for which data was available in Bolivianos (BOB) were

converted into USD using the 2008 exchange rate of 1 BOB equal to US\$0.125.

Bolivia's health care system follows a three-tiered standardized guide for treating diarrhea according to the severity of dehydration: Plan A for mild dehydration, Plan B for moderate dehydration, and Plan C for severe dehydration. Plans A and B can be administered orally over the course of several hours and Plan C is designed to be administered intravenously over 2 days of inpatient care. Three assumptions were made to estimate treatment and diagnostics costs: (1) if a specific Plan was indicated in patient records, all specified components of the Plan were used plus any additional recorded medicines or diagnostics. (2) If no Plan was indicated, but any individual components of intravenous rehydration were recorded, then it was assumed that 1 Plan C package was administered for every 2 days of inpatient treatment. (3) If no Plan or intravenous rehydration was indicated, but specific medications were indicated (5% of records), only those indicated medications were used to calculate cost of treatment.

2.4.2. Hospital outpatient costs

No outpatient visit cost estimates for treatment in a hospital emergency department were available from surveillance facilities; therefore WHO-CHOICE cost estimates for this type of visit were used. Medications, IV rehydration components, medical equipment, and diagnostics ordered for each patient were abstracted using the methods described above. If Plan C was indicated in the records, it was assumed that the cost for an entire Plan C package was incurred. This is due to the fact that a full Plan C package cannot be administered in one day; however, the package components cannot be administered for a second patient and must be discarded if a second day of treatment is not completed.

2.4.3. Outpatient treatment in a non-hospital setting

Because we did not collect data from outpatient treatments of a diarrheal episode in non-hospital settings, we assumed that outpatient treatments in these settings was limited to Plan A. Therefore, we estimated the cost of treatment in this setting as the cost of a Plan A package plus the WHO-CHOICE estimate of an outpatient visit cost in a non-hospital setting [67].

2.5. Vaccine characteristics

National coverage of Diphtheria, Pertussis and Tetanus (DPT) vaccine was used as a proxy for the potential coverage of rotavirus vaccination because the recommended schedule is the same for both vaccines. Data on DPT 1 and 2 vaccination coverage and timing was calculated from the 2003 Bolivia Demographic and Health Survey [71]. Vaccine efficacy was estimated to be 85% against both deaths and hospitalizations due to rotavirus [72]. Because children who are at higher risk for rotavirus mortality are also less likely to receive rotavirus vaccine immunization, the model incorporates a relative coverage correction factor for vaccine efficacy against death. We assumed that vaccine coverage of those most likely to die from rotavirus was 90% of the vaccine coverage of the remainder of the population. Vaccine efficacy against cases requiring outpatient care was estimated to be the average of the efficacy against severe rotavirus illness (85%) and rotavirus illness of any severity (70%) [51,72]. Based on other studies [4,34,37,44,51,73] and confirmed by the Ministry of Health and Sports and the National Rotavirus Surveillance Program, administration costs per dose of vaccine were assumed to be US\$0.50.

2.6. Cost-effectiveness analysis

The primary measurement of cost-effectiveness for this study was the incremental cost-effectiveness ratio (ICER) per DALY

Table 2

Hospitalized and outpatient cases of diarrhea.

	El Alto	La Paz ^a	Cochabamba	Santa Cruz	Bolivia total
Hospital					
% RV positive cases (<i>n</i>)	39.6 (48)	41.1 (90)	42.9 (63)	31.4 (54)	39.2 (255)
Mean months ± SEM (<i>n</i>)	12.7 ± 1.24 (48)	12.7 ± 0.96 (92)	12.2 ± 1.01 (60)	13.1 ± 1.6 (18)	12.6 ± 0.6 (218)
Percent male (<i>n</i>)	69.5 (46)	55.5 (90)	47.8 (69)	58.6 (46)	56.5 (251)
Mean length of stay in days (<i>n</i>)	6.3 (53)	4.7 ^b (100)	4.5 ^b (78)	4.6 ^b (55)	4.9 (286)
Outpatient					
Mean months ± SEM (<i>n</i>)	14.8 ± 0.3 (898)	14.8 ± 0.3 (1082)	12.5 ± 2.1 (17)	15.1 ± 0.1 (2955)	15.0 ± 0.1 (4952)
Percent male (<i>n</i>)	55.7 (896)	55.5 (1083)	56.5 (1120)	55.2 (2952)	55.6 (6051)

^a Cost data were collected at two hospitals for inpatients and one hospital for outpatients in La Paz.^b *p* < 0.05 compared to El Alto.**Table 3**

Average healthcare costs paid by Bolivian healthcare facilities per hospitalized or emergency department patient, stratified by surveillance city.

Mean ± SEM (<i>n</i>)	El Alto	La Paz ^a	Cochabamba	Santa Cruz	Bolivia average
Hospital					
Total bed-day	\$279.99 ± 27.54 (53)	\$210.15 ^b ± 11.86 (100)	\$201.64 ^b ± 13.91 (78)	\$205.19 ^b ± 13.86 (55)	\$219.82 ± 8.21 (286)
Medicines	\$39.18 ± 3.44 (53)	\$29.21 ^b ± 1.46 (100)	\$29.44 ^b ± 1.74 (78)	\$31.59 ± 1.76 (55)	\$31.57 ± 1.03 (286)
Diagnostics	\$10.11 ± 0.79 (53)	\$7.38 ^c ± 0.62 (100)	\$12.06 ± 0.77 (78)	\$7.44 ^c ± 0.81 (55)	\$9.17 ± 0.39 (286)
Total	\$329.28 ± 30.98 (53)	\$246.74 ^b ± 13.31 (100)	\$243.14 ^b ± 15.59 (78)	\$244.22 ^b ± 15.62 (55)	\$260.57 ± 9.25 (286)
Outpatient					
Total	\$16.75 ^c ± 0.05 (901)	\$16.59 ^c ± 0.02 (1085)	\$17.44 ± 0.07 (1134)	\$16.80 ^c ± 0.03 (2960)	\$16.88 ± 0.02 (6080)

^a Data for hospitalized costs were collected at two hospitals in La Paz and one hospital for outpatients.^b *p* < 0.05 compared to El Alto.^c *p* < 0.05 compared to Cochabamba.

averted. A 3% discount rate was utilized for all costs and outcomes. The ICER was calculated using a range of vaccine price between US\$3 and US\$24 per dose. Additional outcome variables calculated include the cost per death averted, the break-even price, and estimates of rotavirus-related events and medical costs averted by vaccination. WHO-CHOICE thresholds are used to define a health intervention as very cost-effective if the cost per DALY averted is less than the GDP per capita of the nation implementing that intervention [67].

2.7. Sensitivity analysis

To assess the combined impact of uncertainty in the input parameters, we conducted a Monte Carlo simulation using Crystal Ball version 11.1.2.1.0 (Oracle, CA). Input ranges were defined for each key input parameter based on ranges in published data (Table 1). The Monte Carlo procedure selects one value from each input distribution and is repeated with 10,000 iterations to construct a distribution of likely outputs. A one-way sensitivity analysis with the same input ranges was also conducted to assess the magnitude of impact of each variable on projected cost-effectiveness utilizing the current vaccine price per dose for Bolivia (US\$9.00).

2.8. Ethical considerations

All portions of the study, including inpatient and outpatient chart abstraction, were approved by Emory University's

Institutional Review Board (Protocol IRB00004406) and the Bolivian National Bioethics Committee prior to data collection.

3. Results

3.1. Study population and economic burden of rotavirus to Bolivia's health care system

Among hospitalized children in our study population, about 40% of patients tested positive for rotavirus infection (Table 2). The average length of hospitalization was 4.9 days. The percentage of rotavirus positive cases was not significantly different between cities with sentinel hospitals. On average, children in El Alto had significantly longer hospital stays than those in other cities. The mean age for children in our study population was 12.6 months among inpatients and 15 months among outpatients.

In Bolivia, the average total cost for hospitalization was US\$260.57 and the average total cost for an outpatient event was US\$16.88 (Table 3). Generally, the total cost per hospitalization was composed of bed day costs (84%), medicines (12%), and diagnostics (4%). Patients in El Alto incurred significantly higher total bed-day and medication costs, likely due to the significantly longer average length of stay in comparison to other sites. Cochabamba patients had significantly higher diagnostic costs compared to La Paz and Santa Cruz, likely because it was the only private hospital sampled, and public hospitals run diagnostic tests for diarrhea cases with less frequency. Outpatient costs per patient were similar across

Table 4

Projected impact of vaccination: estimated rotavirus-related events in the 2003 birth cohort with and without vaccination.

	Events without vaccination	Events with vaccination	Averted by vaccine [95% CL] ^a	% reduction
Outpatient visits	47,560	18,103	29,457 [24,455–31,320]	62
Hospitalizations	9482	3082	6400 [5271–8534]	67
Deaths	813	317	496 [424–658]	61
DALYs	27,753	10,841	16,912 [12,698–19,866]	61
Outpatient direct medical costs	\$589,431	\$224,466	\$364,965 [\$279,613–\$427,084]	62
Hospitalization direct medical costs	\$2,421,400	\$787,561	\$1,633,839 [\$1,123,760–\$2,056,853]	67
Total direct medical costs	\$3,010,831	\$1,012,027	\$1,998,804 [\$1,471,226–\$2,435,146]	66

^a 95% CL were estimated from a multivariate sensitivity model described in Section 2.

Table 5

Estimated costs and cost-effectiveness of universal rotavirus vaccination in the 2003 birth cohort.

	Vaccination cost	Cost per DALY averted [95% CI] ^b	Cost per death averted [95% CI] ^b
At \$3/dose	\$1,619,170.88	CS [CS-\$9.20]	CS [CS-\$312.24]
At \$4/dose	\$2,087,878.24	\$5.27 [CS-\$39.40]	\$179.71 [CS-\$1345.51]
At \$5/dose	\$2,556,585.60	\$32.98 [\$8.70-\$70.40]	\$1125.36 [\$296.24-\$2403.97]
At \$9/dose ^a	\$4,431,415.04	\$143.84 [\$115.10-\$206.50]	\$4907.93 [\$3927.13-\$7051.76]
At \$10/dose	\$4,900,122.40	\$171.56 [\$140.10-\$242.30]	\$5853.57 [\$4779.57-\$8271.05]
At \$15/dose	\$7,243,659.20	\$310.13 [\$262.27-\$421.53]	\$10,581.78 [\$8943.98-\$14,394.06]
At \$20/dose	\$9,587,196.00	\$448.70 [\$381.76-\$601.34]	\$15,310.00 [\$13,020.99-\$20,533.80]

^a Price in Bolivia as of July 2010 is \$9.08.^b 95% CI were estimated from a multivariate sensitivity model described in Section 2. CS: cost savings.

all facilities, although Cochabamba had slightly significantly higher outpatient costs compared to other cities.

3.2. Estimated impact of rotavirus vaccination on the economic burden of rotavirus to Bolivia's health care system

In the absence of vaccination, we estimated that the birth cohort would experience 47,560 outpatient visits, 9482 hospitalizations, and 813 deaths before reaching age 5, accounting for 27,753 DALYs (Table 4). As a result of rotavirus related diarrhea, 189 out of every 1000 children will have received outpatient treatment, 38 out of every 1000 children will have been hospitalized, and 3 out of every 1000 children will die by age 5. From these data, we estimated a rotavirus-associated economic burden of US\$3,010,831 per year from the healthcare perspective (Table 4). In other words, US\$12.00 in direct medical costs will be spent for every child in the cohort. Though the number of outpatient events was about five times higher than hospitalization events, the majority (80%) of Bolivia's economic burden was attributable to events requiring hospitalization.

We estimated that universal rotavirus vaccination, with an estimated coverage based on current national DPT coverage, would reduce outpatient and hospitalization visits, deaths, and DALYs by over 60%. In general, the percentage of events averted increases with vaccination coverage. Notably, we estimated that rotavirus vaccination would reduce annual direct medical costs for rotavirus-associated events by 66%, from US\$3,010,831 to US\$1,012,027.

3.3. Cost effectiveness of rotavirus vaccination

International financial subsidies for Bolivia's rotavirus vaccination program do not provide a sustainable strategy for a permanent rotavirus vaccine program. Bolivia has agreed to contribute 40% of vaccine costs during the first five years of vaccine rollout, eventually moving towards total government financing of the program by 2017 [74]. Given the uncertainty of future vaccination costs, we modeled cost-effectiveness across a plausible range of prices (Table 5). The medical break-even price was calculated at US\$7.62 per vaccine course (2 doses). According to WHO standards for cost-effectiveness, an intervention is very cost-effective if the ICER is less than the GDP per capita and cost effective if the ICER is less than three times a nation's GDP per capita. Utilizing Bolivia's GDP (US\$1758 [75]) as a threshold, rotavirus vaccination is very cost-effective for Bolivia up to a price of US\$67.24 per dose and cost-effective up to a price of US\$194.10 per dose. Using cost per death averted as a measure of cost-effectiveness, rotavirus vaccination would be very cost-effective up to US\$5.66 per dose and cost-effective up to US\$9.38 per dose.

3.4. Sensitivity and uncertainty analysis

To assess which inputs were the most important drivers of cost-effectiveness at Bolivia's current price per dose (US\$9.00), we varied

each individual model input in both one-way (Table 6) and probabilistic multivariate sensitivity (Tables 4–5) analyses. None of the input variations for the sensitivity analysis resulted in cost-savings at the current price of US\$9.00 per dose. In general, ICERs were more affected by variations in the diarrheal mortality (rate of mortality, vaccine efficacy against death) and hospitalization inputs (diarrheal hospitalization rate, hospitalization costs, and vaccine efficacy against hospitalizations) than outpatient inputs (Table 6). Similarly, costs per DALY averted were most sensitive to changes in diarrheal mortality followed by hospitalization inputs, and less sensitive to changes in outpatient inputs (data not shown).

4. Discussion

The goal of this report was to estimate the economic burden of rotavirus and cost-effectiveness of the rotavirus vaccination program in Bolivia for use in policy development as subsidization of universal rotavirus vaccination is withdrawn in 2017. We estimate the annual economic burden of rotavirus at over US\$3 million. We

Table 6
Sensitivity analysis (at \$9.00/dose^a).

Variable	Input value	% change ^b	ICER ^c	% change
Diarrheal mortality rate	0.010	+20	119.92	-17
	0.008	Baseline	143.84	0
	0.006	-20	179.68	+25
Diarrheal hospitalization rate	0.12	+30	114.86	-20.1
	0.0945	Baseline	143.84	0
	0.07	-30	172.82	+20.1
Diarrheal outpatient rate	0.99	+30	137.36	-4.5
	0.7581	Baseline	143.84	0
	0.53	-30	150.32	+4.5
Hospitalization costs ^a	325.71	+25	119.69	-17
	260.57	Baseline	143.84	0
	195.43	-25	167.99	+17
Outpatient costs ^a	21.10	+25	138.45	-4
	16.88	Baseline	143.84	0
	12.66	-25	149.24	+4
Vaccine efficacy against death	0.871	+2.5	140.34	-2.4
	0.85	Baseline	143.84	0
	0.51	-40	239.31	+66.4
Vaccine efficacy against hospitalizations	0.897	+5.5	138.53	-3.7
	0.85	Baseline	143.84	0
	0.51	-40	182.49	+26.9
Vaccine efficacy against outpatient visits	0.823	+5.5	142.65	-0.8
	0.780	Baseline	143.84	0
	0.468	-40	152.50	+6

^a Price in Bolivia as of July 2010 is \$9.08.^b Costs were varied by each event/input costs/rate/efficacy as per ranges specified in Table 1.^c Cost-effectiveness ratio defined as cost per DALY averted (US\$/DALY).

found that rotavirus vaccination reduces, by at least 60%, the number of outpatient visits, hospitalizations, deaths, DALYs, and total direct medical costs associated with rotavirus diarrhea. Further, the rotavirus vaccine was cost-savings below a price of US\$3.81 per dose and cost-effective at Bolivia's current price of \$9 per dose.

The reduction in rotavirus related events and direct medical costs averted are concordant with previously published studies in other lower-middle and upper-middle-income countries [6,29,36,50,51,76]. Our estimation of hospitalization costs per patient (Table 3) is generally higher than published estimates from countries of similar economic status based on GDP per capita, including Vietnam [4], Indonesia [73], and Kyrgyzstan [37]. Our estimate was most similar to published estimates of hospitalization costs in Peru (\$284.08) [36] and Malaysia (\$187.72) [20], both of which have a higher economic status than Bolivia. As expected, hospitalizations exhibited a larger reduction in events (Table 4) and costs (data not shown) than outpatient visits due to the rotavirus vaccine. This is likely due to greater vaccine efficacy against hospitalizations than against diarrheal episodes requiring outpatient treatment (Table 1) and higher hospitalization costs than outpatient visit costs (Table 3).

The estimated break-even price was higher than estimates for countries of similar economic status [51,73], and more similar to the break-even price calculated for some upper-middle-income countries including Chile (US\$10.33 per course [51]) and Panama (US\$7.56 per course [51]). The ICERs for rotavirus vaccination in Bolivia (US\$143.84 per DALY averted at US\$18 per vaccine course) were comparable to ICERs from analyses for countries of similar economic status including Indonesia (\$US120.46/DALY averted at US\$14/course) [73] and low-income Asian countries (US\$212/DALY averted at \$20/course) [6].

If Bolivia were to commit the sum of its current government vaccine expenditures (US\$8,294,595 for 2009 [64]) to universal rotavirus vaccination, it could only afford to purchase the rotavirus vaccine below a price of US\$17.24 per dose (data not shown). Though our model demonstrates cost-effectiveness for even higher prices, this situation is not pragmatic given the numerous essential childhood vaccines that must be considered in the national budget. After the first five years of vaccine rollout subsidized by GAVI, Bolivia will have to allocate a higher percentage of its health systems budget to rotavirus vaccination and re-negotiate rotavirus vaccine prices. Based on our analyses, regardless of the final price Bolivia obtains for rotavirus vaccine, universal vaccination will probably remain a highly cost-effective health intervention. It is important to note that rotavirus vaccination in Bolivia, at the current price of \$9/dose, is comparatively more cost-effective than other most other early childhood health interventions such as expansion of oral rehydration therapy or vitamin A supplementation programs (Table 7). It should also be noted that as vaccine production expands with accelerated introduction into other countries, the price per dose and cost per DALY averter are likely to decrease and cost-effectiveness ratios will improve [34].

Any results of cost-effectiveness analyses are highly dependent on input data variability [78]. For this reason, sensitivity analyses are crucial to addressing the uncertainty of input parameters. While economic analyses of other developing countries also found cost-effectiveness to be most sensitive to mortality and vaccine efficacy inputs [4,6,41,44,45,50,51], it is interesting to note that hospitalization rate and costs are typically more important drivers of cost-effectiveness in countries of higher socioeconomic status than Bolivia [6] due to the higher costs associated with hospitalizations in these countries. It is possible that hospitalization inputs were significant drivers of cost-effectiveness in our study because our estimated costs per hospitalization (US\$260.57) were more similar to costs in higher-income countries than Bolivia. However, our base rates of vaccine efficacy are consistent with previous

Table 7

Comparison of cost-effectiveness ratios of various childhood health interventions to prevent diarrhea mortality for high-mortality nations in the WHO Americas region.

Intervention	ICER ^a	Source
Rotavirus vaccination in Bolivia		
At \$3/dose	CS	This study
At \$4/dose	\$5.27	This study
At \$5/dose	\$32.98	This study
At \$9/dose	\$143.84	This study
At \$10/dose	\$171.56	This study
Oral rehydration therapy expansion to 80%	\$249.00	[67]
Oral rehydration therapy expansion to 95%	\$289.00	[67]
Vitamin A supplementation expansion to 50%	\$209.00	[67]
Vitamin A supplementation expansion to 80%	\$393.00	[67]
Zinc supplementation expansion to 50%	\$43.00	[67]
Zinc supplementation expansion to 80%	\$40.00	[67]

^a Cost-effectiveness ratio defined as cost per DALY averted (US\$/DALY). 95% CL were estimated from a multivariate sensitivity model described in Section 2. CS: cost savings.

studies using similar methodology [4,6,29,37,50,51] and the 95% CL for all the outputs include recent real-world effectiveness studies conducted in high-mortality settings [79,80]. In addition, the range of the estimated percentage of deaths due to diarrhea among under 5 deaths in Bolivia from various sources is 30%: estimates from WHO and PAHO include 7% [81], 15% (used in this model [61]), and 37% [82]. The variation is exacerbated because we have poor estimates for rotavirus-specific mortality. In this study, we utilize the rotavirus-specific hospitalization rate (40%) as a proxy for the rotavirus-specific mortality rate; however, of a small sample of children with acute diarrheal disease who died while receiving treatment in Bolivian surveillance hospitals, 70% were rotavirus positive (communication with Surveillance program staff). Isakbaeva et al. faced an even more difficult challenge in Uzbekistan where there was a 106% variation in rotavirus diarrhea mortality rates depending on the data source [30]. In summary, the sensitivity analysis does not completely capture the possible variation in reported diarrhea mortality in Bolivia.

The main strength of this study lies in the accuracy and validity of the model inputs. For example, we used values for the proportion of pediatric diarrhea hospitalizations due to rotavirus (gleaned from 4 years of national rotavirus sentinel hospital surveillance across multiple geographic regions), direct medical costs (multi-year data collection from all the sentinel hospitals and WHO-CHOICE data) and vaccine efficacy rates (from Rotarix™ clinical trials). To achieve robust cost data, we oversampled both inpatient and outpatient study populations. A second strength was our ability to compare cost data collected through vigorous in-country data abstraction to data available from easily accessible data sources such as WHO-CHOICE. We determined that bed-day costs provided by hospital administration departments were not an accurate reflection of true costs, and therefore WHO-CHOICE was a more reliable cost input (Section 2). Therefore, we examined a range of possible costs in our sensitivity analysis (Table 1) in order to incorporate what was likely the true hospitalization cost.

Our main limitation was that our analyses did not include data on societal costs borne by families of children with rotavirus. One reason for excluding these costs from this analysis was that these costs are not usually an important driver in economic decision-making by the government. However, studies that have included these data along with health care system costs often estimate a higher level of cost-effectiveness [78]. A second limitation is that our study did not incorporate other variables into the cost-effectiveness estimate such as changing recommended age restrictions for rotavirus vaccine administration [83], possible risk of intussusception in certain populations [83], and possible obstacles to rotavirus vaccine efficacy including: varied host protection

with incomplete doses [84,85] and the effect of host nutritional status [86–88]. A third limitation is that our estimations of health care costs and utilization based on the tertiary-level hospitals in the National Rotavirus Surveillance Program likely contributed to higher estimations of costs and cost-effectiveness because more severe cases of diarrhea may present at tertiary hospitals than primary or secondary health facilities. In exchange for this limitation, we were able to directly estimate the proportion of laboratory confirmed rotavirus hospitalization and outpatient diarrhea cases and capture a wide range of variation in utilization and costs in Bolivia based on geographic and climatic region and socioeconomic level of the population served.

In conclusion, we found that incorporating rotavirus vaccination in Bolivia's immunization program is a cost-effective intervention to decrease under-five mortality and morbidity and reduce medical expenditures to the health system. Our model demonstrated that universal rotavirus vaccination averted over 60% of rotavirus related health outcomes and costs and was cost-effective at the current price of \$9 per dose. However, it is important to practically assess Bolivia's ability to fund universal vaccination as international subsidies are gradually withdrawn over the next five years. Our analyses will help guide Bolivia's decision making process as it considers its future allocations for childhood vaccine programs.

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